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ENVIRONMENTAL HAZARD ASSESSMENT REPORT

MAJOR ONE- AND TWO-CARBON SATURATED FLUOROCARBONS

REVIEW OF DATA

August 1976

ENVIRONMENTAL PROTECTION AGENCY
OFFICE OF TOXIC SUBSTANCES
WASHINGTON, D.C. 20460

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This report is a review of the available information on the commercially important one- and two-carbon saturated fluorocarbons (i.e., fluoromethanes and fluoroethanes) pertinent to an assessment of the potential environmental hazard posed by these compounds. Aspects discussed are production, uses, environmental effects and biological effects. Major topics are the potential stratospheric ozone depletion effect from continued emissive uses of certain fluorocarbons and the cardiovascular effects resulting from inhalation of these compounds.

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Major One- and Two-Carbon Saturated Fluorocarbons

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August 1976

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PREFACE

Our society uses thousands of chemical substances with many of them released into the environment in varying quantities as production or handling losses, as waste materials, or as a direct consequence of intended or unintended uses. Concern over possible effects of these chemicals has prompted the establishment of a program by the Early Warning Branch of the Office of Toxic Substances to review release, exposure, and effects data to assist in setting priorities for further study or possible regulatory action.

Detailed analyses on every commercial chemical are not practical. Selected materials are initially screened by a simple literature search and a limited number of these chemicals are selected for more detailed study. Criteria for this selection include volume of production, manner of use, market growth potential, exposure patterns, detection in the environment, known toxic effects, and functional or chemical relationships to known environmental pollutants. The early warning system, which first brings chemicals to the attention of the program uses diverse sources, including opinions of experts, referrals from other units of government, reports in the scientific and trade literature, predictive modelling, and public inquiries. This study was initiated because of the association of fluorocarbons used as aerosol propellants with a number of deaths in recent years of person inhaling aerosol products to achieve an intoxicated state, and because exposure to the fluorocarbons from their use as aerosol propellants was known to be widespread. Additional impetus for this study was the emergence of the theory that continued use of fluorocarbons may result in depletion of stratospheric ozone, with potentially severe effects on life.

These hazard assessments are prepared from reviews of the subject substances supplemented by additional searches and inquiries to obtain the most complete and recent information available.

Only data considered pertinent to an assessment of environmental hazard are reported in this series.

Although the assessment uses as complete an information base as possible, additional information may be available or may become available. Therefore, these assessments are subject to revisions. The Office of Toxic Substances would welcome any additional pertinent data.

Any recommendations in this document are those of the Office of Toxic Substances and may not represent an Agency consensus. Nor do they represent commitment to further action by the Environmental Protection Agency or any other organization. Mention of tradenames and manufacturers of specific products in this document are for purposes of clarity and specificity only and does not constitute an endorsement of any product.

The Environmental Hazard Assessment Series is being prepared under the guidance of Dr. Farley Fisher, Chief of the Early Warning Branch, Office of Toxic Substances. This report was written by Frank J. Letkiewicz.

This assessment was preceded by a general literature review of the fluorocarbons conducted by Dr. Philip Howard and Mr. Patrick Durkin of the Syracuse University Research Corporation, Syracuse, New York, and by a more intensive review of the one and two carbon fluorocarbons conducted by Dr. Philip Howard, Mr. Arnold Hanchett and Mr. Patrick Durkin, again of Syracuse University Research Corporation. The reports which were prepared from these reviews are entitled Preliminary Environmental Hazard Assessment of Chlorinated Naphthalenes, Silicones, Fluorocarbons, Benzenepolycarboxylates and Chlorophenols and Environmental Hazard Assessment of One and Two Carbon Fluorocarbons, both available through the National Technical Information Service, Springfield, Virginia 22151 under NTIS accession numbers PB-238 074 and PB-246 419, respectively.

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SUMMARY

The one- and two-carbon saturated fluorocarbons are organic compounds of the methane and ethane series, respectively, which have one or more fluorine atom substituents. In addition, these compounds may contain chlorine, hydrogen, and/or bromine. The major commercial compounds in this group are (with fluorocarbon number following): trichlorofluoromethane (F-11), dichlorodifluoromethane (F-12), chlorodifluoromethane (F-22), trichlorotrifluoroethane (F-113), dichlorotetrafluoroethane (F-114), chloropentafluoroethane (F-115), chlorodifluoroethane (F-142b), and bromotrifluoromethane (F-13B1). Minor amounts of chlorotrifluoromethane (F-13), tetrafluoromethane (F-14), dichlorofluoromethane (F-21), and trifluoromethane (F-23) are also produced for specialty applications. 2-Bromo-2-chloro-1,1,1-trifluoroethane (halothane) is a widely used anesthetic for surgical procedures.

The fluorocarbons were introduced commercially in the 1930's as non-flammable, non-corrosive, and non-toxic refrigerants and by virtue of these attributes became, as they are today, the mainstay of the refrigeration industry. In the 1950's these compounds were commercialized as propellants for aerosol products, and are today the major, but not the only, class of compounds used for this purpose.

In general the fluorocarbons are volatile substances and display low solubility in aqueous media. They are very stable, often to the point of being referred to as "inert". They are resistant to hydrolysis, oxidation and thermal decomposition except under conditions more severe than those encountered in the environment. Hydrogen-containing fluorocarbons are more readily hydrolyzed and oxidized than are the completely halogenated compounds. The fluorocarbons photodissociate when they are exposed to ultraviolet radiation (wavelength below 220 nm).

The fluorocarbons are produced by fluorination of various chlorocarbons, primarily carbon tetrachloride (CCl_4), chloroform ($CHCl_3$) and hexachloroethane (C_2Cl_6). There are several U.S. producers of fluorocarbons and current total plant capacity is approximately 1.2 billion pounds per year. Domestic production of these compounds is in the area of 900 million pounds per year, of which fluorocarbons 11, 12, and 22 comprise about 90%. Total world production of the fluorocarbons is estimated to be approximately twice that of the U.S.

The major uses of the fluorocarbon compounds are as aerosol propellants, refrigerants, foaming (or blowing) agents for plastic foams, degreasing solvents, fire-extinguishing agents, and as intermediates for the production of polymers. One fluorocarbon, halothane, is a widely used general anesthetic for surgical procedures.

The amount of fluorocarbon which is lost to the environment on an annual basis is difficult to quantify due to uncertainties in the annual losses from refrigerant and closed-cell blowing agent applications. However, because of their volatility and the manner in which these compounds are used, it can be estimated that, except for that used as intermediates, eventually all of the fluorocarbons produced are released to the atmosphere. Aerosol propellants are released directly during use and from the eventual destruction of the cannister. Refrigerants are lost through leakage, during replacement, and from discarded units. Fluorocarbons used as open-cell blowing agents are lost to the environment immediately during use, while closed-cell blowing agents are lost on destruction of the product. Most of the current production of the fluorocarbon degreasing solvent, F-113, is used to replace evaporative losses.

By using extremely sensitive gas-chromatographic methods, fluorocarbons 11 and 12 have been detected in the ambient atmosphere at concentrations of about 100 parts per trillion by volume. These levels, when multiplied by world-wide atmospheric volume roughly correspond to total production of these compounds since they were first commercialized. Increases in atmospheric concentration over recent years similarly correspond to the increases in usage during that time. As would be expected, fluorocarbon levels are higher in areas of high population and industrialization than in rural areas, over oceans, or at high altitudes. Measurements taken near factories using fluorocarbons, in public buildings, homes, and special areas such as beauty parlors show levels somewhat higher than ambient levels. These levels, however, are still in the parts per billion by volume range.

The fluorocarbons, because of their stability, are quite persistent in the environment. Although the hydrogen-containing fluorocarbons are more susceptible to hydrolysis and oxidation than the completely halogenated compounds, it has not been demonstrated that these will be subject to rapid degradation under environmental conditions.

The persistence of the fluorocarbons F-11 and F-12 in the atmosphere was recognized with the earliest reports of environmental detection, but at that time they were considered to pose no hazard to the environment because of their stability and lack of biological effects. In 1974, a theory was put forth which stated that continued release of F-11 and F-12 will cause a depletion of stratospheric ozone. The significance of this lies in the fact that stratospheric ozone acts as a filter which shields the earth from ultraviolet radiation. Because of the harmful biological effects of ultraviolet radiation, it is believed that life as we know it would not exist without the protective ozone shield. The ozone depletion theory states that because of their stability, the fluorocarbons, particularly F-11 and F-12, diffuse into the stratosphere and undergo photolytic decomposition from the high-energy ultraviolet radiation there, which results in the release of chlorine atoms. These chlorine atoms will then react with the ozone (O_3) to convert it to molecular oxygen (O_2). The key aspect of this reaction is that the chlorine, having destroyed an ozone molecule, is returned to react destructively with still more ozone molecules. Because of this catalytic activity, it is believed that a single chlorine atom will destroy many thousands of ozone molecules before the chlorine atom reacts with other substances in the stratosphere which convert it to hydrogen chloride to terminate the sequence. The hydrogen chloride will diffuse back down to the troposphere. The initial calculations based on the ozone depletion theory predicted that continued use of the fluorocarbons would result in 6.5-13% reduction in stratospheric ozone by the middle of the 21st century. Since these initial calculations were made, a number of the key reaction rates and concentrations of important substances in the stratosphere have been refined. The net effect of these refinements has essentially been one of cancellation, and the current predictions of future ozone depletion due to fluorocarbons (7-13%; 8-16%) do not differ significantly from the initial estimates.

Although it is clear that the presence of ozone in the stratosphere is essential for the continuance of life, the consequences of partial ozone depletion and a concomitant increase in ground-level ultraviolet radiation are not known in detail. Most of the concern has focused on a possible increase in skin cancer among humans. There is also concern that increased ultraviolet radiation will result in increased skin cancer among domestic animals. Other studies indicate the possibility of reduction in plant growth, interference with photosynthesis, and mutations in plants. Climatological changes, including alterations in temperature distribution and rainfall patterns, are also considered to be possible. Except perhaps for the increases in skin cancer, the magnitude of biological and climatological consequences of increased ultraviolet radiation due to ozone depletion are presently hypothetical. Furthermore, accurate predictions of the extent to which such effects might occur as the result of a partial ozone depletion are not currently possible.

The ozone depletion predictions have prompted an interagency task force to recommend that fluorocarbon applications resulting in their release to the atmosphere be banned by 1978 unless information emerges which indicates gross inaccuracies in the current models. Both the Federal government and industry are sponsoring research aimed at determining the validity of the fluorocarbon-initiated ozone depletion theory, and studies on the impact of partial ozone depletion on man and his environment are to be pursued. Studies are also being undertaken to identify possible alternatives for F-11 and F-12 and of the potential economic and social disruptions which would accompany fluorocarbon restrictions.

In addition to the concern for stratospheric ozone depletion due to fluorocarbons, there has also been some concern regarding the direct health effects of these compounds. The fluorocarbon aerosol propellants have been responsible for several deaths when they were intentionally inhaled by individuals attempting to achieve an intoxicated state. The cause of death was probably cardiac arrhythmia, aggravated by elevated blood levels of epinephrine due to stress and/or an increase in blood carbon dioxide. The fluorocarbon anesthetic halothane has been associated with liver injury, headache, and mood alterations in patients, and with liver injury, spontaneous abortion and congenital abnormalities in chronically exposed operating room personnel. Studies have shown that inhaled fluorocarbons are rapidly absorbed into the blood and under conditions of continuous exposure they can enter certain tissues. When exposure is terminated, the fluorocarbons are rapidly eliminated through exhaled air with no indication that they accumulate in any tissue. Limited data indicate that some metabolism to carbon dioxide (about 1%) may occur with F-11 and F-12. The metabolism of the fluorocarbon anesthetic halothane to compounds which bind covalently to cell lipid and protein has been demonstrated. The formation of bound metabolites has been associated with the liver toxicity of this and other compounds. Limited data indicate that inhaled F-11 and F-12 may also result in some cellular binding. More detailed studies on the formation of bound metabolites from the commercially important fluorocarbons are needed. Such studies are also indicated for the hydrogen-containing fluorocarbons which have been suggested as replacements for F-11 and F-12 since these are structurally similar to halothane.

In laboratory animals, the acute lethality of inhaled fluorocarbons is very low, with F-11 and F-113 being lethal at 5-25% in air and the other fluorocarbons being fatal only at concentrations of 40% to 80% or more. Acute inhalation studies on the ability of the fluorocarbons to produce cardiac arrhythmias, as well as their effects on other cardiovascular and respiratory parameters have shown that F-11 and F-113 are the most toxic of the commercially significant fluorocarbons. F-11 and F-113 produce cardiac arrhythmias, sensitize the heart to epinephrine-induced arrhythmias, and influence other cardiac parameters. Some studies have demonstrated that animals with diseased cardiac and respiratory systems are more sensitive to the acute cardiovascular and respiratory effects of the fluorocarbons than healthy animals. A possible increase in sensitivity to the fluorocarbons in humans with cardiac or respiratory illness may exist, but this is difficult to determine definitively on the basis of these animal studies.

Except for halothane and one 10-month study with F-22, the "chronic" toxicity testing of the fluorocarbons has thus far been limited to periods of 90 days or less. While no remarkable toxicological consequences have been reported in these studies, pathological changes in the liver and inflammatory infiltration of the lung have been observed in some studies. Chronic inhalation of 10 ppm halothane in rats has been shown to result in ultrastructural changes at the cellular level in the liver, kidney and central nervous system. Offspring of exposed pregnant rats have been found to have similar ultrastructural changes and also decreases in performance on behavioral tests. Long-term exposure studies of adult and developing animals to the commercially important fluorocarbons in the parts per million range utilizing electron microscopic examination of cell structures as in these halothane studies are needed to assess the chronic toxicity of these compounds.

I. INTRODUCTION

During the decades surrounding the turn of the century, scientists and engineers worked tenaciously toward the production of a practical mechanical refrigeration device. While a machine essentially the same as that which is used today existed in 1928, no completely satisfactory substance was available for use as the refrigerant. Of the compounds proposed at that time, all had serious disadvantages: ethylene was flammable; sulfur dioxide was corrosive and toxic; ammonia possessed all three of these drawbacks; and carbon dioxide required bulky equipment to handle the necessary high pressures. To make the mechanical refrigeration devices commercially feasible, an acceptable refrigerant had to be found. This material had to have the necessary physical properties, yet be non-flammable, non-corrosive, and non-toxic. In 1930, a group of scientists commissioned by the General Motors Corporation announced that a compound meeting all these criteria had been found. The compound was dichlorodifluoromethane, CCl_2F_2, and its introduction marked the birth of the fluorocarbon industry.

While the fluorocarbon refrigerant market was quite successful, it was not long before the industry received a significant boost stemming from the development of aerosol insecticides during World War II. Because of their chemical inertness and negligible toxicity, along with their suitably high vapor pressures, certain fluorocarbons were the materials of choice for use as propellants for these aerosol products. Commercialization of aerosols began in the early 1950's and today there are innumerable items available as aerosols using fluorocarbon propellants.

Today, the major commercial fluorocarbons are trichlorofluoromethane (CCl_3F), dichlorodifluoromethane (CCl_2F_2), chlorodifluoromethane ($CHClF_2$), trichlorotrifluoroethane ($C_2Cl_3F_3$), dichlorotetrafluoroethane ($C_2Cl_2F_4$), chloropentafluoroethane (C_2ClF_5), chlorodifluoroethane ($C_2H_3ClF_2$), and bromotrifluoromethane ($CBrF_3$). 2-Bromo-2-chloro-1,1,1-trifluoroethane (CF_3-$CHBrCl$), also known commonly as halothane, is a widely used general anesthetic. Minor amounts of chlorotrifluoromethane ($CClF_3$), tetrafluoromethane (CF_4), dichlorofluoromethane ($CHCl_2F$), and trifluoromethane (CHF_3) are also produced for specialty applications. The major uses of the fluorocarbons remains in the refrigerant and aerosol propellant areas.

The virtual non-toxicity and inertness of these compounds, which made them so attractive in their applications, have come under question recently, and their environmental safety, so long assumed, has been challenged on two fronts. It has been hypothesized that the two fluorocarbons produced in the greatest amounts, trichlorofluoromethane and dichlorodifluoromethane, can effect a depletion in the ozone levels of the stratosphere. Because of the protection which stratospheric ozone affords to life on earth, the Federal Task Force on the Inadvertent Modification of the Stratosphere (IMOS) has concluded in a report on the fluorocarbon/ozone problem that the continued release of these compounds to the environment is a legitimate cause for concern, and has recommended that, unless new data emerge which remove the cause for concern, trichlorofluoromethane and dichlorofluoromethane uses be restricted by 1978 to those not resulting in release to the environment. In addition to the ozone question, there has also been some concern for the direct effects of the fluorocarbons on human health because of deaths in recent years among individuals intentionally inhaling fluorocarbon-propelled aerosol products for the purpose of achieving an intoxicated state. This paper will consider these topics and others relevant to the evaluation of the environmental safety of the fluorocarbons.

Throughout this paper a standard shorthand numerical system will be used to identify the compounds, rather than the often cumbersome chemical nomenclature. The numerical system consists of a four-digit number, ABCD, where D is the number of fluorine atoms in the molecule, C is the number of hydrogen atoms in the molecule plus 1, B is the number of carbon atoms minus 1, and A equals the number of double bonds in the molecule. Whenever A or A and B are zero, the digits are omitted from the number. When bromine is substituted for chlorine, a B plus the number of bromine atoms follows the number of fluorine atoms (e.g., $CClF_3$ is 13 whereas $CBrF_3$ is 13B1). The fluorocarbon numbers are preceded by the letter "F" or, in the refrigeration industry, "R". This is to avoid confusion with a second system (the Halon system) often used for the bromine containing fire-extinguishing agents. In the Halon system ABCD signify the number of carbon, fluorine, chlorine and bromine atoms, respectively, and the number is preceded by the letter "H". Fluorocarbon numbers are given for the major one and two carbon saturated fluorocarbons in Table D-I (Appendix D.).

II. STRUCTURE, PROPERTIES, AND REACTIVITY

The fluorocarbons under discussion are one- or two-carbon saturated compounds containing fluorine. The compounds may also contain chlorine, bromine, and/or hydrogen atoms.

Chemical formulae and some physical properties of the commercially important fluorocarbon compounds are shown in Table I. Typical characteristics of the fluorocarbon compounds are high vapor pressure, low boiling point, high density, and low water solubility. The degree of fluorine substitution affects the physical properties. Generally, as the number of fluorine atoms replacing chlorine atoms in the molecule increases, the vapor pressure goes up, while the boiling point, density and the solubility decrease. Bromine atoms tend to increase the density and lower the vapor pressure.

The major applications of the fluorocarbons, as refrigerants and aerosol propellants, are based on their chemical stability rather than their reactivity. This stability is due largely to the strength of the C-F bond and the increase in the C-Cl bond energy associated with increased fluorine substitution. Although they are often referred to as "inert", the fluorocarbons, like other halogenated organic compounds, may react violently with highly reactive materials and should not be exposed to alkali or alkaline earth metals (sodium, potassium, barium, etc.).

Most of the common construction metals, such as steel, copper, aluminum, etc., are compatible with the fluorocarbons. The more reactive metals, such as zinc, magnesium, and aluminum alloys containing more than 2% magnesium, may be used with the fluorocarbons under anhydrous conditions. They are not recommended for use with fluorocarbons where water or alcohol are present.

The fluorocarbons exhibit low rates of hydrolysis, usually too low to be determined when water alone is used. The presence of metals or, in the case of hydrogen-containing fluorocarbons, alkaline conditions will tend to increase the rates of hydrolysis.

Table I

Molecular Formulae and Physical Properties of Commercially Important Fluorocarbons

		Fluorocarbon Number						
	11	12	13	22	113	114	115	13B1
Molecular Formula	CCl_3F	CCl_2F_2	$CClF_3$	$CHClF_2$	$C_2Cl_3F_3$*	$C_2Cl_2F_4$**	$CClF_2$-CF_3	$CBrF_3$
Molecular Weight	137.37	120.92	104.5	86.47	187.38	170.93	154.47	148.92
Boiling Point (1 atm) °C °F	23.82 74.87	-29.79 -21.62	-81.4 -114.6	-40.75 -41.36	47.57 117.63	3.77 38.78	-39.1 -38.4	-57.75 -71.95
Freezing Point °C °F	-111 -168	-158 -252	-181 -294	-160 -256	-35 -31	-94 -137	-106 -159	-168 -270
Vapor Pressure, psia (at 25°C)	15	92	510	150	6.4	31	130	230
Solubility of Co d in water, wt. % (1 atm, 25°C)	0.11	0.028	-	0.30	0.017 (sat'n pres.)	0.013	0.006	0.03
Density, liquid g/cc (25°C) lbs/ft³	1.476 92.14	1.311 81.84	- -	1.194 74.53	1.565 97.69	1.456 90.91	1.291 80.60	1.538 96.01
Density, Sat'd Vapor g/l	5.86	6.33	-	4.72	7.38	7.83	8.37	8.71
(at boiling point) lbs/ft³	0.367	0.395	-	0.295	0.461	0.489	0.522	0.544

* Predominately CCl_2F-$CClF_2$ (Hamilton, 1962)

** Predominately $CClF_2$-$CClF_2$ (Hamilton, 1962)

The fluorocarbon compounds are highly resistant to attack by conventional oxidizing agents at temperatures below 200°C (Bower, 1971; Downing, 1966).

Because of the presence of a hydrogen atom in the molecule, fluorocarbons such as F-22, F-142b and F-152a are probably more susceptible to hydrolysis and oxidation than the completely halogenated fluorocarbons (Hamilton, 1962). Whether hydrogen-containing fluorocarbons are subject to hydrolytic or oxidative degradation under environmental conditions has yet to be adequately demonstrated. One study by Cox et al. (1976) discussed in Section V.C. does indicate that F-142b reacts with ·OH radical (simulating photochemical oxidation) whereas F-11 and F-12 do not.

The fluorocarbons also have a high degree of thermal stability, with the more highly fluorinated compounds being generally more stable. Specific rates of thermal decomposition depend on experimental conditions and the presence of contaminants such as air or water. Thermal stability data have been presented by Callighan (1971) and DuPont (1969).

Photodissociation of the fluorocarbons occurs when they are irradiated with ultraviolent light with wavelengths below 200 nm. Because of the possible effects of this reaction on stratospheric ozone, it is dealt with in more detail in the context of that problem in Section VI. The lack of photolysis of fluorocarbons with longer wavelengths of light under conditions simulating photochemical smog is discussed in Section V.C.

III. PRODUCTION

A. Production Methods

The most widely used method for commercial synthesis of the major fluorocarbons consists of the catalytic displacement of chlorine in chlorocarbons by fluorine from reaction with anhydrous hydrogen fluoride (Hamilton, 1962). The commonly used chlorocarbons are carbon tetrachloride (CCl_4), chloroform ($CHCl_3$), and hexachloroethane (C_2Cl_6). A more recent process developed by DuPont in the U.S. and Montecatini Edison in Italy uses the direct reaction of methane with a mixture of chlorine and hydrogen fluoride.

The several steps in the conventional chlorocarbon process are shown in Figure 1. The reaction phase uses antimony pentachloride as a catalyst and some chlorine gas which maintains the catalyst in its pentavalent rather than its trivalent state. The reaction can be conducted in either liquid or vapor phases.

The liquid-phase operation is carried out by feeding liquid hydrogen fluoride (HF) and chlorocarbon to the reactor and simultaneously withdrawing hydrogen chloride (HCl) and the desired organic product as vapor from the top of the reflux condenser. Reaction conditions can vary from pressures of 0 to 500 psig, temperatures of 45° to 200°C, catalyst concentrations from 10 to 90 weight per cent, and take-off temperatures of -30 to +100°C (Hamilton, 1962). The liquid process is characterized by simple and flexible operation. The quick removal of final product avoids overfluorination.

The vapor-phase process consists of a heated tube filled with a granular catalyst. The feed is a vaporized mixture of HF and chlorocarbons. The process is frequently used for the production of the highly fluorinated compounds.

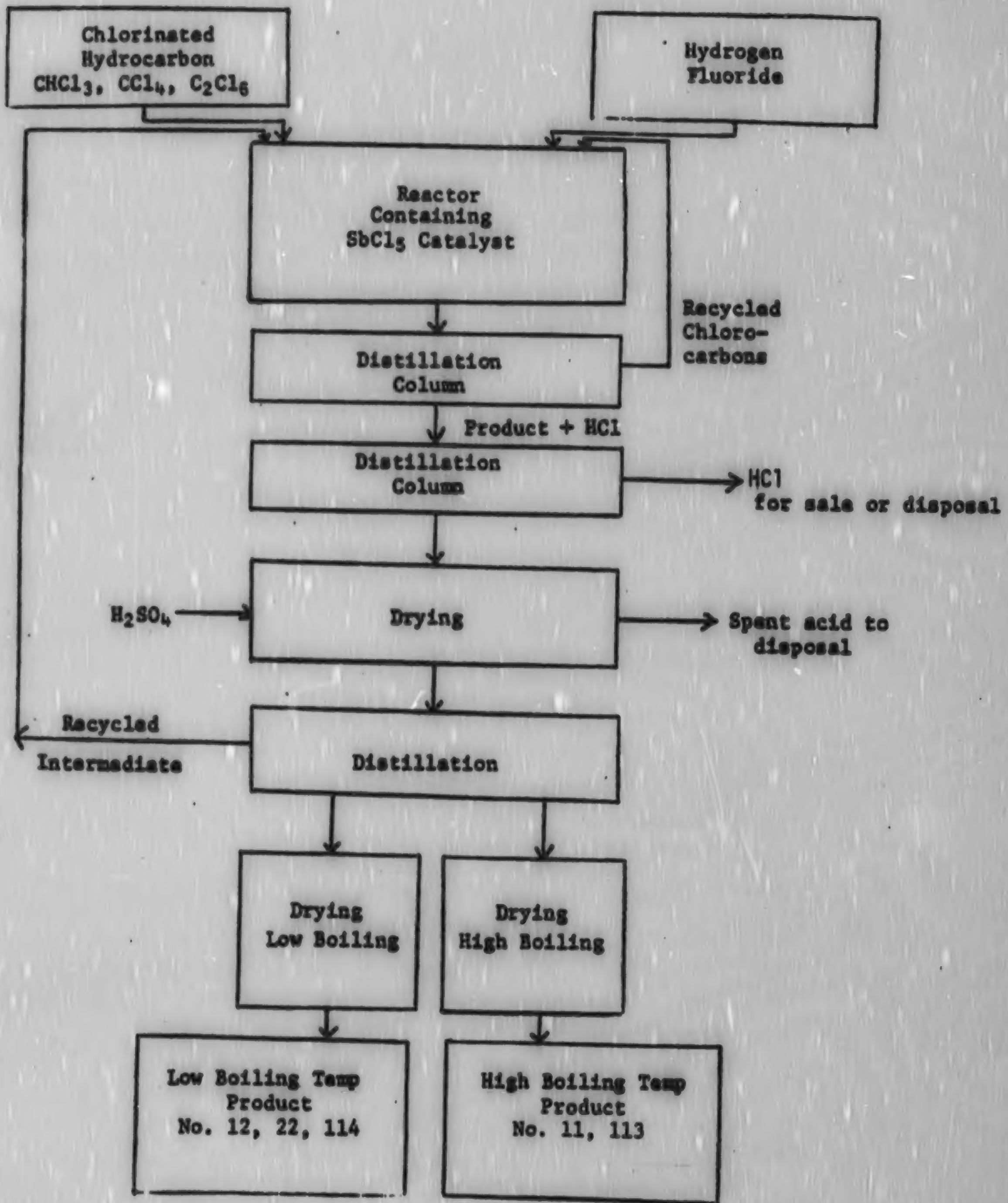
Chlorinated Hydrocarbon $CHCl_3$, CCl_4, C_2Cl_6
Hydrogen Fluoride
Reactor Containing $SbCl_5$ Catalyst
Recycled Chloro-carbons
Distillation Column
Product + HCl
Distillation Column
HCl for sale or disposal
H_2SO_4
Drying
Spent acid to disposal
Recycled Intermediate
Distillation
Drying Low Boiling
Drying High Boiling
Low Boiling Temp Product No. 12, 22, 114
High Boiling Temp Product No. 11, 113

Figure 1

Flow Diagram of Fluorocarbon Manufacture from Chlorinated Hydrocarbons

In both processes, the proportion of the mixed fluorinated products is determined by the chlorocarbon used and by the temperature, pressure, and reaction time. By-product hydrogen chloride can be separated either by distillation or by scrubbing. The distilled hydrogen chloride has the advantage of being extremely pure and, therefore, can be used directly in some associated synthesis or packaged for sale. Unreacted hydrogen fluoride may also be recovered.

Bromotrifluoromethane is made by a similar process, starting with carbon tetrabromide. However, it can also be made by the bromination of trifluoromethane or by the replacement of chlorine in chlorotrifluoromethane by reaction with hydrogen bromide.

Fluorocarbon production equipment is generally conventional in design, using standard distillation columns, scrubbers, and drying towers. The reactors are jacketed or tubular vessels made of carbon or stainless steel. Since the reaction is slightly endothermic, heat is supplied by steam, by flue gas, or by electrical heaters.

B. Producers

The major U.S. producers are listed in Table II along with the trade names and numbers of their fluorocarbon products and an estimate of total plant capacities (Directory of Chemical Producers, 1975; U.S. International Trade Commission, 1973).

Table III presents a list of foreign manufacturers of fluorcarbons.

C. Quantity Produced and Price

The reported total demand for all fluorocarbons in the U.S. was 945 million pounds in 1974 and 805 million pounds in 1975 (Chemical Marketing Reporter, 1975). Total U.S. demand in 1973 was 880 million pounds (Chemical Marketing Reporter, 1973). The world production of fluorocarbons is approximately twice the U.S. production (McCarthy, 1974).

U.S. production and market values in recent years for F-11, F-12, and F-22 are shown in Table IV; production estimates for other fluorocarbons are included in Table V. Estimated production of F-114 for 1972 was 20

Table II: Fluorocarbon Producers and Plant Capacities

Company	Trade Name	Total Plant Capacity Millions of lbs./yr.	Major Fluorocarbon Compounds Produced
Allied Chemical Corporation	Genetron®	310	11, 12, 22, 113, 114, 152a
E.I. duPont de Nemours & Co.	Freon®	500	11, 12, 13, 14, 22, 113, 114, 115, 142b, 152a, 13B1
Kaiser Aluminum and Chemical Corporation	Kaiser	50	11, 12, 22
Pennwalt Chemical Corp.	Isotron®	115	11, 12, 22, 142b
Racon, Inc.	Racon®	20	11, 12, 22
Union Carbide Corporation	UCON®	200	11, 12

Table III: Foreign Fluorocarbon Producers

Country	Producer	Trade Name
Argentina	Ducilo S.A.	Freon
	Fluoder S.A.	Algeon
	I.R.A.S.A.	Frateon
Australia	Australian Fluorine Chemicals	Isceon
	Pacific Chemical Industries	Foran, Frigen
Brazil	DuPont do Brasil	Freon
	Hoechst do Brasil Quimica e Farmceutica	Frigen
Canada	DuPont of Canada	Freon
	Allied Chemical (Canada)	Genetron
China	(State authority)	---
Czechoslovakia	Slovek Pro Chemickov A Hutni Vycbu, Ustinad Cabem	Ledon
England	Imperial Chemical Industries	Arcton
	I.S.C. Chemicals	Isceon
France	Produits Chimiques Pechiny-Ugine-Kuhlman	Forane
	Rhone-Poulenc Industrie	Flugene
East Germany	V.E.B. Chemiewerk Nunchritz	Frigedohn
West Germany	Chemische Fabrik von Heyden AG	(sold by Hoechst)
	Farbwerke Hoechst AG	Frigen
	Kali-Chemi Pharma Gmbh	Kaltron
Greece	Chemical Industries of Northern Greece	F-11, F-12
India	Everest Refrigerants	Everkalt
	Navin Fluorine Industries	Mafron
Israel	Makhtsim-Daron (subsid. Koor Chemicals)	
Italy	Montedison	Algofrene
Japan	Mitsui Fluorochemicals Co.	Freon
	Daikin Kogyo Co.	Daiflon
	Asahi Glass Co.	Asahiflon
	Showa Denko K.K.	Flonshowa
Mexico	Halocarburos S.A.	Freon
	Quimobasicos	Genetron
Netherlands	DuPont (Nederland)	Freon
	Akzo Chemie B.V.	FCC
Rumania	(State authority)	---
South Africa	African Explosives & Chemical Industries	Arcton
Spain	Ugimica	Forane
	Kali-Chemie Iberia	Kaltron
	Hoechst Iberica	Frigen
U.S.S.R.	(State authority)	Eskimon

Table IV

Production of Fluorocarbons 11, 12 and 22 in the U.S. and Market Value

Compound (Fluorocarbon #)	Trichlorofluoromethane (11)		Dichlorodifluoromethane (12)		Chlorodifluoromethane (22)	
	Production (10^6 lb)	Price (dollars/lb)	Production (10^6 lb)	Price (dollars/lb)	Sales (10^6 lb)	Price (dollars/lb)
1961	91	—	173	—	24	—
1962	125	—	208	—	29	—
1963	140	—	217	—	36	—
1964	148	—	228	—	43	—
1965	170	—	271	—	50	—
1966	170	—	286	—	56	—
1967	182	—	310	—	59	—
1968	204	—	326	—	55	—
1969	238	.18	368	.25	71	.56
1970	244	.19	375	.26	73	.51
1971_p	258	.19	390	.25	80	.51
1972_p	300	.18	439	.24	80	.49
1973_p	334	.19	488	.24	102	.45
1974_p	341	.24	487	.31	112	.56

Source: U.S. International Trade Commission (1961-1974)

p - Preliminary

Table V

Uses of Fluorocarbons in the United States (1972)

Fluorocarbon Number	Fluorocarbon Formula	Production[d] 1972 (10^6 lbs.)	Aerosol Propellant %[b]	Aerosol Propellant Quantity (10^6 lbs.)	Refrigerants %[b]	Refrigerants Quantity (10^6 lbs.)	Solvents %[b]	Solvents Quantity (10^6 lbs.)	Foaming Agent %[b]	Foaming Agent Quantity (10^6 lbs.)	Fire Extinguishing Agent %[b]	Fire Extinguishing Agent Quantity (10^6 lbs.)
11	CCl_3F	300[a]	82	246	3	9			15	45		
12	CCl_2F_2	439[a]	60	264	30	132			10	44		
22	$CHClF_2$	80[a,b]			100	80						
113	$CClF_2CFCl_2$	~50[c]					100	~50				
114	$CClF_2CClF_2$	~20[c]	95	19	5	1						
115	$CClF_2CF_3$	~10[c]	10	-	90							
1301	$CBrF_3$				5						95	~4
Total		~900		529		221		50		89		~4
% of Total Production[e]		-		59%		25%		5%		10%		

[a] U.S. International Trade Commission, 1972.

[b] Sales

[c] Estimates based upon discussions with DuPont and Allied Chemical; 1973 and 1974 production of F-113 approximately 60 million lbs./year (Shamel et al., 1975).

[d] The production figures only marginally consider amounts used in the manufacture of fluorocarbon plastics. Fluorocarbon 22, 113, and 114 are used to synthesize the plastics. However, 13 million lbs. of polytetrafluoroethylene was produced in 1972 (U.S. International Trade Commission) from fluorocarbon 22, but that quantity is not reflected in the 80 million lbs. sales figure.

[e] The Chemical Marketing Reporter (1975) reports the following percentage of use: propellants-50%; refrigerants-28%; plastics-10%; solvents-5%; blowing agents, exports, miscellaneous-7% on a 1975 total production of 805 million lbs. The percentages reported in this table are similar in magnitude but quantitatively differ mostly because plastics have not been included.

million pounds, as shown in Table V; Shamel et al. (1975) estimated that production of F-114 was 25 million pounds in 1972, and 27 million pounds in 1974. Production data for individual fluorocarbons are not available for 1975; however, the U.S. International Trade Commission reports that combined production of F-11 and F-12 was approximately 602 million pounds for the period January through November, 1975.

Hoffman (1976) has estimated the 1975 worldwide production of three minor fluorocarbons F-13, F-14, and F-21 to be 110,000-440,000 pounds, 30,000-120,000 pounds and 30,000-120,000 pounds, respectively. No information was available on the annual production of halothane, the widely used fluorocarbon anesthetic.

From 1968 through 1974, U.S. fluorocarbon production increased at an annual rate of 11%; 1974 production is believed to have increased only 4.5% over 1973 levels (Stanford Research Institute, 1975). The Chemical Marketing Reporter (1975) predicts no net growth for 1974-1978.

Because of the theory that continued use of the two major fluorocarbons, F-11 and F-12, may result in a significant decrease in stratospheric ozone (see Section VI), other fluorocarbons are being investigated as possible replacements for these two compounds. The leading candidate substances are, reportedly, F-22 (already produced in substantial quantity for refrigeration), F-133a (CF_3-CH_2Cl), F-142b ($CClF_2$-CH_3), F-152a (CHF_2-CH_3) and a number of compounds in the F-120 series (fluoroethanes containing one hydrogen atom) (Anonymous, 1976).

IV. USES

The major uses of the fluorocarbon compounds are as aerosol propellants, refrigerants, and foaming agents. Certain of the fluorocarbons have major uses as solvents, as fire extinguishing agents, or as intermediates in the production of fluorocarbon resins and plastics. The use pattern of the fluorocarbons is shown in Table V, where polymer intermediate uses are not included since the available production figures do not encompass this application.

The largest commercial use of the fluorocarbons is as propellants in aerosol* products. The aerosol packaging industry began during World War II, when two USDA researchers found that the efficiency of insecticides was significantly increased when they were mixed with the fluorocarbons, and dispensed as fine microscopic droplets. Civilian commercialization began in the early 1950's, and today the world production of aerosol products is about 6 billion units per year, with the U.S. accounting for about half of the total. About half of all aerosol products are fluorocarbon propelled; more than 75% of the fluorocarbon-propelled aerosol products are for personal use (deodorants, hair care, etc.), with the remainder being household products, insecticides, coatings, and other industrial and commercial items (Shamel _et al_., 1975). Fluorocarbon 115 is approved for use as an aerosol propellant in food products.

Use as refrigerants is the next largest application of the fluorocarbons and is the use for which the fluorocarbons were originally commercialized in the 1930's. The fluorocarbons are used for both refrigeration (localized low temperature cooling) and air-conditioning (cooling of rather large volumes of environmental air). A distinction can be made between the large commercial units, which

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* The term "aerosol" is used to include any "self-dispensing, pressurized, self-propelling products dispensed by the use of a liquefied, non-liquefied or noncondensed gas" (Sage, 1963).

are charged after the units are in place, and the smaller prefabricated units which are charged and sealed at the factory. The difference between the prefabricated and large commercial units is important in terms of the environmental release of the fluorocarbon refrigerants. Table VI divides the use of the three major refrigerants, F-11, 12, and 22, into the above categories for 1972 from information supplied by Hanavan (1974). F-13 is used in low temperature specialty refrigeration applications employing reciprocal compressors and in the low temperature segment of cascade refrigeration systems. F-14, and possibly F-13B1 are also used in the low-temperature segment of cascade refrigeration systems. The only known use for F-21 is as a conventional refrigerant for cabin cooling in the NASA space shuttle (Hoffman, 1976).

Blowing agents are used in the plastics industry to produce a finished product in a foamed or expanded form. The fluorocarbons were first used in the production of polyurethane foams, where they impart improved thermal insulation properties because of the fluorocarbon trapped in the cells of the finished product. Fluorocarbons are also used to form open-cell foams, in which case they are released to the air. Blowing-agent uses of the fluorocarbons are divided approximately equally between closed- and open-cell applications.

The higher-boiling fluorocarbons, especially F-113, find use as selective solvents for cleaning precision equipment and for extraction of a variety of natural products. Some fluorocarbon solvents are azeotropes or blends with non-fluorocarbons, such as F-113 and dichloroethane (azeotrope); F-113, methylene chloride and cyclopentane (azeotrope); F-113 and SDA-30 alcohol (azeotrope); and F-113 and isopropyl alcohol (blend).

F-22, F-113 and F-142b are used as intermediates in the production of fluorocarbon resins. F-22 is pyrolyzed to produce tetrafluoroethylene, which is polymerized to form polytetrafluoroethylene (PTFE). PTFE is

Table VI

Use of Fluorocarbon Refrigerants

Fluorocarbon		Quantity Used as Refrigerant	Air Conditioning				Refrigeration			
			Prefabricated		Large Commercial		Prefabricated		Large Commercial	
Formula	Number	(10^6 lbs.)	%	Quantity 10^6 lbs.	%	Quantity 10^6 lbs.	%	Quantity 10^6 lbs.	%	Quantity 10^6 lbs.
CCl_3F	11	9	-	-	72%	6	-	-	28%	3
CCl_2F_2	12	132	45% (automobiles)	59	29%	38	7%	9	19%	25
$CHClF_2$	22	80	57%	46	41%	33	-	-	2%	2
		221		105		77		9		30

% Prefabricated = 52%

% Large Commercial = 48%

the major fluorocarbon resin produced, accounting for about 80% of all fluorocarbon resins in 1970. Production of PTFE in 1974 was 18.4 million pounds, which requires approximately 30 million pounds of F-22. Hexafluoropropylene is also derived from F-22 and is used as a copolymer with tetrafluoroethylene to produce fluorinated ethylene-propylene resins and with vinylidine fluoride to produce a vinylidine fluoride-hexafluoropropylene copolymer. Vinylidine fluoride is a pyrolysis product of F-142b. Dechlorination of F-113 with zinc produces chlorotrifluoroethylene, which is used to produce polychlorotrifluoroethylene, and also as a copolymer with vinylidine fluoride to produce a chlorotrifluoroethylene-vinylidine fluoride resins.

The fluorocarbon resins are used in a number of mechanical, electrical, and chemical applications where their properties of strength, chemical inertness, weatherability, resistance to temperature extremes, nonflammability, low coefficient of friction (non-stick properties), and excellent dielectric properties are of advantage. The amount of fluorocarbons used as plastic intermediates is not known, but it has been estimated to be 50-100 million pounds for 1972 over and above the 900 million pound total shown in Table V (Howard _et al._, 1974).

Use of fluorocarbons as fire-extinguishing agents is a relatively small application of these compounds. The only fluorocarbon used to any extent as a fire extinguishing agent in the U.S. is F-13B1 ($CBrF_3$), while F-12B1 ($CBrClF_2$) is used widely in Europe and Australia. F-13B1 is an effective agent for surface fires, as with flammable liquids, and on most combustible solids, excepting some of the active metals, metal hydrides, and materials containing their own oxidizer (Hammack, 1971). In general, these compounds appear to have good application in situations where the value density is high, such as in aircraft, spacecraft, mines, and computers (Jensen, 1972).

Halothane (CF_3-CHBrCl) is a widely used general anesthetic for surgical procedures. No information was available on the volume of halothane used in the U.S. annually. Russell (1976) estimates that about 25 million anesthetics are administered annually in the U.S., and that 50% or more are with halothane. Usage has declined steadily since the mid-1960's due to medical-legal concerns stemming from reports of various toxic effects both to patients and operating room personnel.

Some of the minor applications of the fluorocarbons are uses as dielectric fluids, heat-transfer fluids, power fluids, cutting fluids, pressurized leak-testing gases, gases in wind tunnels and bubble chambers, and as a drain opener propellant (DuPont, 1969; Dowing, 1966).

The projected growth markets for the fluorocarbons are as heat and power transfer fluids (especially if adopted for use in the Rankine cycle engine); as a dry-cleaning solvent (F-113); as an immersion freezing agent for food (F-12); and increased use as intermediates for fluorocarbon resins and elastomers (Drysdale, 1971; Noble, 1972).

V. ENVIRONMENTAL ASPECTS

A. Release to the Environment

The total amount of fluorocarbons produced annually in the U.S. is currently greater than 900 million pounds, predominantly fluorocarbons 11, 12, and 22 (see Tables IV and V). The major routes by which the fluorocarbons reach the environment involve their commercial applications. Further, all losses of the fluorocarbons are to the atmosphere. Fluorocarbon losses have been estimated to be less than 1% during production operations and less than 1% during storage and transport (McCarthy, 1973). While 1% translates to roughly 9 million pounds per year, which is a considerable amount of material, it is practically insignificant when compared to total environmental losses described below.

Estimating the annual release of fluorocarbons from their commercial uses is difficult due largely to uncertainties in the rate of fluorocarbon losses from the refigerant applications. In the refrigerant use, especially when prefabricated, sealed appliances such as home refrigerators, freezers, and air conditioners are considered, there is a significant time delay (10 years or more) between production of the refrigerant and disposal of the appliance when corrosion, damage, etc. result in release of the refrigerant to the atmosphere. Large commercial and industrial refrigeration and air conditioning units are subject to losses from leakage during their lifetime and require recharging to replace lost refrigerant. Of the refrigerant loss estimates which have been reported (Howard _et_ _al_., 1974; Howard and Hanchett, 1975; Shamel _et_ _al_., 1975), that of Shamel _et_ _al_. (1975) considers the problem in most detail. These authors calculated that, in 1973, a total of 212.3 million pounds of fluorocarbon was lost to the environment from refrigerant uses.

All of the fluorocarbon which is used as an aerosol propellant is released to the environment. About 1% or less is lost during charging and sealing of the containers (Harmon, 1974), and the remainder is lost during the actual use of the aerosol product or from the destruction and eventual corrosion of the discarded containers. It is estimated that there is a delay of approximately one year between production and release to the atmosphere from aerosol products. Therefore, losses in 1973 are approximately equal to 1972 aerosol propellant consumption, or about 500 million pounds. The fluorocarbons which are of most importance in environmental contamination by this pathway are F-11 and F-12.

The rate of loss of fluorocarbons from solvent uses, primarily F-113, is also difficult to estimate because of uncertainty in the amount recovered for reuse. Information presented by DuPont (1975) indicates that the current growth of F-113 solvent uses (i.e., for new equipment other than replacement of scrapped units) is negligible. Hence, the annual loss rate is probably close to the annual production, or 50-60 million pounds in 1973.

Loss of fluorocarbons used as blowing agents is estimated to be about 100% from open-cell foams, and negligible from closed-cell foams. Since the fluorocarbon blowing agents are approximately equally divided between open-cell and closed-cell applications, losses are about 50% of the annual blowing-agent demand.

Except for polymer intermediate uses, fluorocarbons will also be lost to the environment from the minor applications, although it is impossible to estimate such losses on an annual basis.

Using the above information, it is estimated that more than 700 million pounds of fluorocarbon was emitted from U.S. applications in 1973. Assuming that the future U.S. consumption pattern remains constant, future annual losses will probably continue to be equivalent to about 80% of production in that year. Worldwide emissions, as with production, are approximately twice those for the U.S.

While estimates of annual loss rates are useful guides, they should not overshadow the point that, eventually, all of the fluorocarbon produced (with the exception of that used as an intermediate) will be released to the environment as either the direct (as with aerosol propellants) result of the applications for which they are produced or the eventual disposal of the products in which they are incorporated.

Because of the characteristic high vapor pressures, low boiling points, and low water solubilities of this class of compounds and because all losses are initially to the atmosphere, it would be expected that released fluorocarbons would be present primarily in the air. This is shown to be the case by actual measurements, which are described below.

B. Methods of Analysis and Environmental Detection

The method most often used to detect fluorocarbons in the air at low levels is direct analysis of air-fluorocarbon mixtures using gas chromatography with an electron capture detector (GC-EC). This technique, which is specific for halogenated compounds, is extremely sensitive to F-11, being typically capable of detecting it at 5-10 ppt v/v (parts per trillion by volume). This method can also typically detect F-12 at 100 ppt v/v (Hester et al., 1974). Recently, Hester et al. (1975b) reported improvements in the GC-EC techniques which make it possible to routinely measure F-11 at 1 ppt v/v and F-12 at 10 ppt v/v. For fluorocarbons with fewer than two chlorine substituents, or with more fluorine and hydrogen substituents (such as F-22, F-115), the sensitivity of GC-EC falls off. For these compounds, gas-chromatography with a flame-ionization detector is as sensitive as GC-EC (Clemons and Altschuller, 1966). Unlike electron capture, however, flame-ionization is not specific for halogenated compounds. Lillian et al. (1975) have used a gas chromatography with both an electron capture detector and flame ionization detector for simultaneous measurement of a number of halocarbons, including fluorocarbons, in atmospheric samples.

Gimsrud and Rasmussen (1975) have used a gas chromatograph linked directly to a mass spectrometer for measuring F-11 and F-12 in atmospheric samples. This method has approximately the same sensitivity as GC-EC for F-11 and F-12 (5 ppt v/v for each), and offers the advantage of giving positive identification of the sample components from the mass spectra.

Hanst et al. (1975) have used long path infrared absorption spectroscopy to measure the fluorocarbons in atmospheric samples. The method offers no advantages over the others in sensitivity and air samples must be concentrated (Hanst et al. use a cryogenic procedure) to permit detection of the fluorocarbons. The method is useful, however, for verifying the identity of substances measured by gas chromatography.

While production and release of the fluorocarbons, especially F-11 and F-12, have been significant since the early 1950's, detection of fluorocarbons in the environment did not occur until 1970. Although some F-12 measurements have been reported, the fluorocarbon most often measured is F-11. This is due largely to the availability of the GC-EC method which, as mentioned above, is extremely sensitive to F-11. Published F-11 and F-12 measurements are shown in Table VII. The levels of F-11 over urban areas are several times those levels found in rural areas and over oceans. This is not surprising since the primary mode of F-11 entry into the environment is from aerosols and refrigeration devices, use of which is, of course, much greater in areas of high population and industrialization.

The data of Wilkness et al. (1975) for Washington, D.C. show high levels of F-11 during stagnant air conditions, with a decrease as clean air arrives and displaces the polluted air mass. From another point of view, Lovelock's data (1971; 1972) for a rural area in southwest Ireland show low levels of F-11 when winds are from the Atlantic Ocean, but the levels increase when polluted air arrives from the European continent with easterly winds.

TABLE VII

Atmospheric Concentrations of Fluorocarbons 11 and 12

Site, Date, and Conditions	Concentration (parts per trillion by volume) F-11	F-12	References
Urban Sites:			
Los Angeles Basin, July 25, 1972 (inversion layer present)	560	700	Hester *et al.*, 1974
Los Angeles Basin, Sept - Oct, 1972 (various conditions)	650	-	Simmonds *et al.*, 1974
San Diego, California (downtown), 1973	290± 240	3200± 1400	Su and Goldberg, 1973
LaJolla Pier, (San Diego), Calif., 1973	370± 560	5800± 4600	Su and Goldberg, 1973
Washington, D.C., July 9, 1974 (air pollution conditions)	380	-	Wilkness *et al.*, 1975
Washington, D.C., July 11, 1974 (advancing Canadian cold front)	200	-	Wilkness *et al.*, 1975
Washington, D.C., July 12, 1974 (following Canadian cold front passage)	160	-	Wilkness *et al.*, 1975

TABLE VII (cont.)

Atmospheric Concentrations of Fluorocarbons 11 and 12

Site, Date, and Conditions	Concentration (parts per trillion by volume) F-11	F-12	References
Ocean Sites:			
Atlantic Ocean, voyage from United Kingdom to Antartica, and return, 1971-1972	49.6± 7.1 (~80 ppt above 40°N; ~50 ppt at 20°N; ~40 ppt between 0°-60°S)	-	Lovelock *et al.*, 1973
Atlantic Ocean, voyage from Hamburg to Santo Doming, October, 1973	88.6± 4.05	115.2± 33.1	Lovelock, 1974
Pacific Ocean, November - December, 1972	~70 at 20°N ~65 at 0° ~60 at 60°S	-	Wilkness *et al.*, 1973
Pacific Ocean, March - April, 1974	~87 at 20°N ~80 at 0°	-	Wilkness *et al.*, 1975

The F-11 levels found over the Atlantic and Pacific Oceans indicate the ubiquity of this compound in the atmosphere. Wilkness et al. (1975) have compared their data over the Pacific for 1972 and 1974 with the Atlantic data of Lovelock for 1971-1972 and have calculated that the background level of atmospheric F-11 increased 22% between November 1971 and November 1972, 31% between November-December 1972, and March-April 1974, with an overall increase of 60% between November 1971 and March-April 1974. These increases are proportional to the estimated world-wide production and release increase of F-11 during these periods. The ocean data also indicate higher levels in the northern hemisphere than in the southern hemisphere, which is to be expected since the major use areas of F-11 (North America, Europe) lie in the northern hemisphere.

Lovelock et al. (1973) and Wilkness et al. (1975) have reported the presence of F-11 in ocean surface waters. The F-11 was not measured as the concentration within the water in either case, but was instead measured as the aerial concentration above the water sample after equilibrium was achieved. While these measurements do indicate that some F-11 is present in the well-mixed surface waters of the ocean, the significant finding was that no F-11 was detectable in samples taken from below the surface waters (about 200 meters depth) indicating that the oceans are not a significant sink for F-11.

Of special interest in considering environmental exposure to the fluorocarbons are the levels which occur at or near the sites where fluorocarbons are released. Hester et al. (1974) measured F-11 and F-12 levels proximal to two factories known to use these compounds. Near a cosmetics plant where fluorocarbon-propelled aerosol cans are filled, levels were 3-4 times the typical city readings. Near a polyurethane plant (blowing agent use), concentrations of F-11 which were detected (24-42 ppb v/v) were 100 times the average city readings.

Hester et al. (1974) also examined F-11 and F-12 levels in homes and in public buildings. In homes, F-11 concentrations ranged from 0.3 to 510 ppb v/v. While F-11 and F-12 concentrations in homes were generally higher than levels outside the home, there was no "typical level" in the homes nor were exceptional levels detected in any particular room. Levels in public buildings where fluorocarbons are apt to be used (drug store, beauty shop, hospital, etc.) were also higher than outside air levels, and, except for the high levels found in the beauty shop (50 ppb v/v F-11; 370 ppb v/v F-12), the levels were similar to the home samples.

Bridbord et al. (1974) presented data showing that the F-12 level in a 29,300-liter room during a 60-second release of hair spray was 62,100 ppb, falling off to 2,500 ppb in 30 minutes and 100 ppb in 60 minutes. Air sampled in a 21,400-liter room one minute after a 30-second release of an insect spray had an F-12 level of 466,400 ppb, declining to 26,400 ppb after 60 minutes and 11,500 ppb after 150 minutes.

C. Environmental Fate of Fluorocarbons

A boundary occurs in the earth's atmosphere known as the tropopause, the height of which varies with latitude, season and particular weather conditions. Near the polar regions the height of the tropopause may be only 8 kilometers, increasing to about 18 kilometers in tropical regions. Below the tropopause is the portion of the atmosphere known as the troposphere which is characterized by a monotonic decrease in temperature with increasing altitude. Above the tropopause and extending to an altitude of about 50 kilometers is the portion of the atmosphere known as the stratosphere where temperature increases with increasing altitude, although the maximum temperature reached at the top of the stratosphere is still less than 0°C. Within the troposphere there are no apparent sinks for the fluorocarbons. While there is no published information on the bioaccumulation or biodegradability of the fluorocarbons, the volatility and general resistance of these compounds to metabolism and biotransformation would limit, if not preclude, interactions in the biosphere as sinks for the fluorocarbons. [Unpublished data indicate that soil and plant uptake of F-11 and F-12 is not significant (Taylor, unpublished).]

Although F-11 and F-12 are detectable in the well-mixed surface waters of the oceans, the levels found eliminate the oceans as a significant fluorocarbon sink (Lovelock et al., 1973; Wilkness et al., 1975).

Using wavelengths above 310 nm, Japar et al. (unpublished) found no evidence of reaction with fluorocarbons 11, 12, 113, 114, and 115 during irradiations of mixtures of the fluorocarbons with olefins and nitrogen oxides in a long-path infrared cell reaction vessel. Hester et al. (1974) placed F-11 and F-12 in ambient air samples in a 20-liter Pyrex carboy and irradiated them for a period of almost two months with eleven blacklight fluorescent lights; they found no detectable change. Hester et al. (1975b), using identical procedures but including F-113 and F-114 in the sample, were again unable to detect any loss of fluorocarbon. Hester et al. (1975b) detected no loss of fluorocarbon in an air sample containing F-11, F-12, F-113, F-114, propene, and nitrogen dioxide irradiated with simulated sunlight for seven hours. Addition of sulfur dioxide and irradiation for up to seven days resulted in aerosol formation, but again no detectable loss of fluorocarbon. Saltzman et al. (1966) found no photochemical reactivity for F-13B1 irradiated with fluorescent blacklights.

Cox et al. (1976) have measured the reactivity of F-11, F-12, F-142b, and other halocarbons with hydroxyl radical, ·OH. (Photooxidation of hydrocarbons is primarily initiated by the reaction with ·OH.) F-11 and F-12 were essentially unreactive with ·OH. The calculated tropospheric lifetimes with respect to oxidation by ·OH were much greater than 1000 years for F-11 and greater than 330 years for F-12. The calculated lifetime of F-142b, a hydrogen-containing fluorocarbon, was 8 years. For comparison, the lifetimes of chloro-, dichloro-, and trichloromethane were 0.37, 0.30, and 0.19 years, respectively.

The persistence of the fluorocarbons, particularly F-11 and F-12, is further demonstrated by the fact that currently measured concentrations of these compounds in the troposphere roughly account for all of these materials produced to date, given the uncertainties in the assumed volume of the atmosphere, in the non-uniform global distribution of the compounds, and in the worldwide release estimates which are introduced into the calculations (Howard and Hanchett, 1975; Lovelock _et al._, 1973; Wilkness _et al._, 1973). These claims imply that the tropospheric lifetimes of F-11 and F-12 are at least 40 years (the span of production of the fluorocarbons) and are possibly infinite. Sze and Wu (1975) argue that the current tropospheric levels of F-11 and F-12 are also consistent with lifetimes of only 10-20 years, since most of the production and release of these materials has occurred in the past 20 years (approximately 98% for F-11 and 92% for F-12). Still, no tropospheric sinks have been found for F-11 or F-12 that could support lifetimes shorter than 40 years. Krey _et al._ (1976), using measured stratospheric and tropospheric concentrations, industrial production rates, and a photolysis half-life of 2-4 years in the stratosphere, calculated the total atmospheric half-life of F-11 to be 15-30 years.

The environmental fate of the fluorocarbons other than F-11 and F-12 has not been reported in the literature. Although the hydrogen-containing fluorocarbons are expected to be more susceptible to hydrolytic and photooxidative degradation than the perhalogenated compounds (Hamilton, 1962), it has yet to be shown that these compounds will degrade readily in the troposphere.

While the persistence of the fluorocarbons in the troposphere was recognized with the earliest reports of detection, it was assumed then that because of their high degree of stability, the fluorocarbons presented no threat to the environment. A theory has recently emerged which suggests that these compounds will diffuse upward into the stratosphere and will catalytically destroy stratospheric ozone. The mechanism and significance of this possible adverse environmental effect of the fluorocarbons follows.

VI. STRATOSPHERIC OZONE DEPLETION FROM FLUOROCARBONS

Ozone, O_3, is a natural minor ingredient of the earth's atmosphere found predominantly in the stratosphere in a layer between about 15 and 50 kilometers above the earth's surface, maximizing at about 25 kilometers. Although referred to as the "ozone layer" it should be pointed out that this is by no means a region of pure ozone. Even at the 25-kilometer altitude of maximum occurence, the density of ozone does not exceed 10^{13} molecules per cubic centimeter. Compared to approximately 10^{18} molecules of air per cubic centimeter at this altitude, the peak ozone mixing ratio is less than 10 ppm by volume. The ozone layer acts as a filter, shielding the earth's surface from practically all solar radiation of wavelengths shorter than 300 nm, *i. e.*, ultraviolet light.

The mechanism by which ozone is produced in the atmosphere was first described by Chapman (1930). The two-step scheme he proposed, as shown in reactions [1] and [2], involves the photolysis of molecular oxygen by radiation of wavelengths below 242 nm, and the subsequent combination of the atomic oxygen formed in [1] with molecular oxygen, involving a third body, M, which is usually N_2 or O_2.

$$O_2 \xrightarrow{\text{u.v. radiation}} 2O\cdot \qquad [1]$$

$$O\cdot + O_2 + M \rightarrow O_3 + M \qquad [2]$$

Ozone is destroyed, according to Chapman, by reactions [3] and [4].

$$O_3 \xrightarrow{\text{u.v. radiation}} O_2 + O\cdot \qquad [3]$$

$$O_3 + O\cdot \rightarrow 2O_2 \qquad [4]$$

Reaction [3] occurs primarily with radiation of wavelengths below 300 nm.

Ozone can also be destroyed by a catalytic reaction with naturally occurring nitric oxide as shown in reactions [5] and [6]. This sequence, identified by Crutzen (1970), is referred to as the "NO_x" cycle.

$$NO + O_3 \rightarrow NO_2 + O_2 \qquad [5]$$

$$NO_2 + O\cdot \rightarrow NO + O_2 \qquad [6]$$

The NO_x cycle is considered to be the most important natural control of ozone levels in the stratosphere. Recently, there has been concern that supersonic transport planes will inject significant amounts of nitrogen oxides into the stratosphere and upset the natural balance of the cycle, perhaps resulting in ozone depletion.

An ozone reduction sequence similar to the NO_x cycle occurs with natural odd-hydrogen species (H, $\cdot OH$, HO_2), but is not significant compared to the NO_x cycle.

A chain reaction sequence resulting in ozone destruction involving chlorine atoms, as shown in reactions [7] and [8], was investigated by Stolarski and Cicerone (1974) and Wofsy and McElroy (1974).

$$Cl\cdot + O_3 \rightarrow ClO + O_2 \qquad [7]$$

$$ClO + O\cdot \rightarrow Cl\cdot + O_2 \qquad [8]$$

This "ClX" cycle may also interact with the NO_x cycle thus:

$$ClO + NO \rightarrow Cl\cdot + NO_2 \qquad [9]$$

$$NO_2 + O\cdot \rightarrow NO + O_2 \qquad [6]$$

$$Cl\cdot + O_3 \rightarrow ClO + O_2 \qquad [7]$$

Initially, the ClX cycle was not considered important since no major source of Cl· entry into the stratosphere was known. Molina and Rowland (1974), noting the measurements of Lovelock *et al*. (1973) and their own work on photochemistry, proposed that the flourocarbons, particularly F-11 and F-12, constitute a significant source of chlorine entry into the stratosphere. The basis of this theory is that these compounds, because of their high degree of stability in the troposphere, diffuse upward into the stratosphere where (unlike in the troposphere) sufficient ultraviolet radiation of wavelengths lower than 220 nm exists, and are thus photolysed, resulting in the release of free chlorine atoms. The fluorocarbons may supply enough chlorine to the stratosphere for the ClX cycle to surpass the NO_x cycle as the primary mechanism of ozone destruction. Further, there is concern that, as a result, an overall depletion of the amount of ozone in the stratosphere will ensue.

It is evident from the measurements of F-11 and F-12 in remote areas that these two compounds are very stable and mobile in the troposphere and would, therefore, most probably persist long enough to diffuse upward into the stratosphere. Although actual measurements of the fluorocarbons in the stratosphere are limited (Table VIII), these data clearly demonstrate that the fluorocarbons do in fact reach the stratosphere. An older data point for stratospheric F-11 and F-12 has been reported recently. Murcray (1975) reexamined data taken in 1968 at 60,000 ft. (about 18.3 km) by balloon over New Mexico and reported that F-11 and F-12 concentrations at that time were 20 ppt and 50-60 ppt, respectively. According to Murcray, this represents an annual increase of about 14 percent, similar to the annual increase in fluorocarbon use. Because extensive data on stratospheric levels are not available, it has been necessary to rely upon atmospheric diffusion models, or, more specifically, the sets of empirical equations which describe the transport of trace substances in the atmosphere, to predict the stratospheric concentration of fluorocarbons. Although diffusion models involving all three dimensions (vertical, longitudinal,

TABLE VIII

STRATOSPHERIC MEASUREMENTS OF F-11 AND F-12

Altitude (km)	Date	Concentration (ppt v/v) F-11	 F-12	References
40-50	5/23/73	<0.2	< 5	Heidt *et al.*, 1975[a]
34	5/7/74	3	35	Heidt *et al.*, 1975[a]
31	5/7/74	9	48	Heidt *et al.*, 1975[a]
28.6	6/2/75	11	--	Heidt *et al.*, 1975[a]
26.2±1	n.s.	<20	75±5	Schmeltekopf *et al.*, 1975[b]
24.5	6/2/75	18	--	Heidt *et al.*, 1975
23	9/9/73	45	86	Heidt *et al.*, 1975
22.3±.7	n.s.	30+3,-6	135±10	Schmeltekopf *et al.*, 1975
~18.3	5/23/74	57	110	Hester *et al.*, 1975a[c]
17.7±.5	n.s.	80±10	210±10	Schmeltekopf *et al.*, 1975
16.9	6/2/75	95	--	Heidt *et al.*, 1975
~12.2	5/23/74	75	140	Hester *et al.*, 1975a
10	6/74	70-80	--	Lovelock, 1974[d]
9	6/74	70-95	--	Lovelock, 1974[d]
8.5	6/74	70	--	Lovelock, 1974[d]

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a) Measurements taken over eastern Texas; tropopause at 15-17 km.
b) Measurements taken over Wyoming; tropopause at ~15 km.
c) Measurements taken over New Mexico/Colorado; tropopause height not stated.
d) Measurements taken over United Kingdom; tropopause at ~8.5 km.

and latitudinal) have been developed, the one-dimensional (vertical) models have been used for the fluorocarbon considerations. These one-dimensional models involve the concept of a "global average eddy diffusion coefficient," the value of which is generally adjusted to fit observations of average mixing patterns of some trace species in the atmosphere. The predicted altitude profile of fluorocarbons (and the photodissociation products) will, of course, depend on the diffusion model which is used.

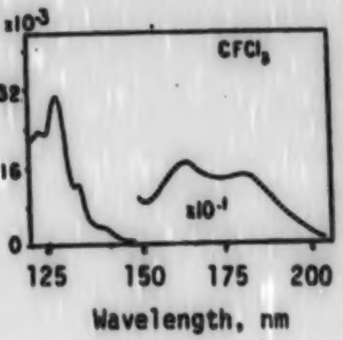
It was mentioned earlier that the fluorocarbons F-11 and F-12 will undergo photochemical decomposition when exposed to radiation in the ultraviolet region, but that this process did not occur in the troposphere since appreciable amounts of the necessary radiation do not penetrate to the troposphere. In the stratosphere, sufficient ultraviolet radiation is available for the photolytic reaction and there is a competition between upward diffusion and photodissociation of the fluorocarbons.

Doucet et al. (1973) have determined the ultraviolet absorption spectra for a series of chlorofluoromethanes. The spectra for F-11 and F-12 are shown in Figures 2 and 3. While these compounds are subject to dissociation by the entire range of wavelengths up to about 220 nm, Rowland and Molina (1974) point out that the slow diffusion of these compounds into the stratosphere, together with the strong absorption of the lower wavelengths in the photodissociation of O_2 (reaction [1]) at higher altitudes probably limits the fluorocarbon-dissociating wavelengths to a band between 184-220 nm.

The photodissociation rates (or absorption cross-sections) of the fluorocarbons have been shown recently to be temperature dependent (Rebbert and Ausloos, 1975). The values used in the following models are those taken at room temperature; the effect of the temperature dependence modification is discussed later.

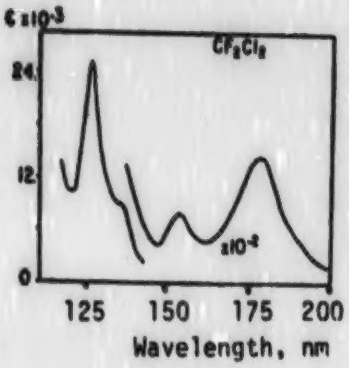
The photochemical process resulting in dissociation, as shown in reactions [10] and [11], has been interpreted as involving a transition

Figure 2 (Doucet, *et al*., 1973)



The vacuum ultraviolet spectrum of $CFCl_3$. The ϵ values of the two lowest frequency bands are multiplied by 100.

Figure 3 (Doucet, *et al*., 1973)



The vacuum ultraviolet spectrum of CF_2Cl_2. The ϵ values of the lowest frequency bands are multiplied by 100.

to a repulsive electronic state that results in immediate dissociation of the carbon-halogen bond. The energy available from the 184-220 nm wavelengths far exceeds that required for C-Cl cleavage and is sufficient to dissociate the C-F bonds as well. There is no information showing that the C-F bonds are broken competitively with the C-Cl bonds, and most researchers have assumed that the primary photochemical decomposition of fluorocarbons follows that shown in reactions [10] and [11], with loss of one chlorine atom. Rebbert and Ausloos (1975) have reported that absorption of low wavelength (i.e., high energy) ultraviolet radiation may result in the release of two chlorine atoms from each F-11 or F-12 molecule per photon.

$$CFCl_3 \xrightarrow{\text{u.v. radiation}} CFCl_2 + Cl \qquad [10]$$

$$CF_2Cl_2 \xrightarrow{\text{u.v. radiation}} CF_2Cl + Cl \qquad [11]$$

Rowland and Molina (1974) found that the best estimate of the quantum yield (*i.e.*, the measure of the efficiency of the photodissociation reaction taken as the number of molecules of starting material changed per photon of radiation of a specified wavelength absorbed) at 213.8 nm for reaction [10] is 1.0 0.1, and that the quantum yield for reaction [11] at 184.9 nm is also 1.0. Quantum yields of unity have been confirmed at 184.9 nm by Milstein and Rowland (1975) and at 213.9 nm by Pitts *et al*. (1974). A quantum yield of unity indicates an efficient photolytic reaction.

If two chlorine atoms are released from F-11 and F-12 directly from photolysis, as proposed by Rebbert and Ausloos (1975) with low wavelength ultraviolet, the residual molecules are CFCl and CF_2, respectively. Although relatively stable, these species may react with oxygen and are currently being investigated by the above researchers.

If only one chlorine is released upon photolysis, the residual $CFCl_2\cdot$ and $CF_2Cl\cdot$ radicals, from F-11 and F-12 respectively, probably form phosgene type molecules. Marsh and Heicklen (1965) found that F-11 photolyzed in the presence of O_2 produced substantial amounts of $CFClO$ and that the yield was unaffected by varying the $CFCl_3/O_2$ ratio from 0.1 to 10. The mechanism of $CFClO$ formation is not known, but probably involves a transient intermediate, $CFCl_2O_2$ which may decompose directly to $CFClO$ and ClO or react by some other pathway to yield $CFClO$ and $Cl\cdot$ or ClO. Similarly, photolyzed F-12 should yield CF_2O plus either $Cl\cdot$ or ClO. (Since $Cl\cdot$ and ClO rapidly interchange under stratospheric conditions as in reactions [7] and [8], the exact species formed is of no consequence.)

The photodissociation of F-11 or F-12 would result in the formation of two ClX molecules ($Cl\cdot$ or ClO), either directly from photolysis or one from photodissociation and one from the reaction of the residual radical with O_2. The possible fate of the $CFClO$ and CF_2O molecules may be additional direct solar photodissociation, chemical reaction with various radical species, hydrolysis, or downward diffusion and eventual tropospheric rainout. In many of the models it is assumed that half of the $CFClO$ produced by photodissociation of F-11 undergoes further reaction releasing the $Cl\cdot$ atom, while half diffuses to the troposphere, resulting in a ratio of 2.5 $Cl\cdot$ atoms per molecule of F-11 initially photolyzed.

The chlorine which is released into the stratosphere from fluorocarbons may enter into the reaction sequence as shown in [7] and [8].

$$\begin{array}{ll} Cl\cdot + O_3 \rightarrow ClO + O_2 & [7] \\ \underline{ClO + O \rightarrow Cl\cdot + O_2} & [8] \end{array}$$

$$\text{Net:}\quad O_3 + O \rightarrow 2O_2$$

This is, of course, a chain reaction in which ozone (or more specifically, total odd-oxygen* species $O_3 + O\cdot$) is catalytically destroyed.

There are other possible $Cl\cdot$, ClO reactions in the stratosphere affecting odd-oxygen removal. ClO may react with NO as in reaction [9]:

$$ClO + NO \rightarrow Cl\cdot + NO_2 \qquad [9]$$

This reaction, competitive with [8], will depend on the $O\cdot/NO$ ratio at the altitude where it occurs. The fraction of ClO reacting with $O\cdot$ increases with altitude (where the $O\cdot$ concentration is greater), so that reaction [9] is significant only at lower altitudes. The effect of reaction [9] on odd-oxygen removal depends upon the fate of the NO_2 formed. Reacting with $O\cdot$ as in [6] results in an overall depletion of two odd-oxygen equivalents. (This is the interaction of the ClX and NO_x cycles.) However, because of the low concentration of $O\cdot$ at the 25-35 km altitude where the NO concentrations are significant, this reaction is not favored, but rather the photolysis of NO_2 to $NO + O\cdot$, with no overall net change in odd-oxygen concentration is likely to occur.

Free $Cl\cdot$ may react with both stable (CH_4, H_2, HNO_3, etc.) and radical (HO_2) hydrogenous materials. Of the possible reactions, only those with CH_4, H_2, and HO_2 are currently thought to be of importance. These reactions, [12]-[14], all forming HCl, terminate, at least temporarily, the ClX chain reaction with odd-oxygen species. Rowland and Molina (1974) have concluded that the only reactions for

$$CH_4 + Cl\cdot \rightarrow HCl + CH_3\cdot \qquad [12]$$
$$H_2 + Cl\cdot \rightarrow HCl + H\cdot \qquad [13]$$
$$HO_2 + Cl\cdot \rightarrow HCl + O_2 \qquad [14]$$

* It is often convenient to consider variations in the sum of O_3 and $O\cdot$, the "odd-oxygen" species, rather than O_3 alone.

terminating the ClX cycle are those producing HCl, which is removed from the stratosphere by downward diffusion and tropospheric rainout. Recently it was postulated that ClO reacts in the stratosphere with NO_2 to form chlorine nitrate, $ClNO_3$, which would diminish the ozone depleting effect of ClX (and also NO_x). This possibility was considered after a reported winter measurement showed only half the amount of HCl in the stratosphere as predicted by the models and seen in measurements taken during other seasons. Initial calculations based on estimates of the rate of formation and destruction of chlorine nitrate indicated that significant amounts could be formed. However, as more data were obtained, it became apparent that chlorine nitrate could play at most only a minor role in stratospheric chlorine chemistry. Because chlorine nitrate has characteristic infrared absorption peaks, Dr. Philip Hanst of EPA at Research Triangle Park, N.C. examined stratospheric infrared spectra taken by Dr. David Murcray and colleagues at the University of Denver to determine if chlorine nitrate were present in the stratosphere. No significant amount of chlorine nitrate was found. Furthermore, the anomalous HCl data that sparked the interest in chlorine nitrate were found to be in error by a factor of 2.2. Correcting these data by this factor places them in agreement with other HCl data. Thus, formation of HCl remains the only known important reaction terminating the ClX cycle for ozone removal (Cicerone, 1976).

Formation of HCl does not necessarily terminate the ClX cycle permanently, however, since it can be renewed by the reactions shown in [15]-[17]:

$$HCl + \cdot OH \rightarrow H_2O + Cl\cdot \qquad [15]$$

$$HCl + O\cdot \rightarrow \cdot OH + Cl\cdot \qquad [16]$$

$$HCl \xrightarrow[(220\ nm)]{u.v.\ radiation} H + Cl\cdot \qquad [17]$$

The extent to which ClX species are involved in the odd-oxygen depletion reactions is determined by the time spent as Cl· and ClO versus the time spent as HCl. The Cl·/ClO and the HCl/ClO ratios are approximated by equations (1) and (2), respectively (Rowland and Molina, 1974):

$$\frac{[Cl\cdot]}{[ClO]} = \frac{k_8[O\cdot] + k_9[NO]}{k_7[O_3]} \qquad (1)$$

$$\frac{[HCl]}{[ClO]} = \frac{\Sigma k_x[HX]}{k_7[O_3]} \quad \frac{k_8[O\cdot] + k_9[NO]}{k_{15}[\cdot OH]} \qquad (2)$$

where $\Sigma k_x(HX)$ is the summed reaction rates for Cl· reaction with CH_4, H_2, and HO_2; numeric subscripts for the rate constants (k) refer to the reaction involved. Crutzen (1974) included reactions [16] and [17] in his estimate of HCl concentrations. Table IX shows the solutions to equations (1) and (2) at various altitudes and the data used for the calculations. As shown in Table IX, HCl is the dominant species at all altitudes. However, the rate of Cl· removal by reaction with O_3 is far more rapid (estimated to be 10,000 times more rapid at 30 km) than by the combined HCl producing reactions.

It was noted earlier that sufficient ultraviolet radiation exists to cleave C-F bonds as well as C-Cl bonds, so that the fate of F· atoms must also be considered. Stolarski and Rundel (1975) have examined the effect of fluorine atoms on ozone in an manner analogous to the studies of the effects of the chlorine atoms. The reactions of F· with H_2 and CH_4 resulting in the formation of HF are much more rapid than the corresponding reactions for Cl· shown in [12] and [13]. Once formed, HF is not readily destroyed by chemical reaction or photodissociation. Reaction with ·OH is endothermic and the most likely pathway of HF destruction to give F· is reaction with $O(^1D)$, which is about two orders of magnitude more effective than photodissociation of HF. The catalytic efficiency of ozone reduction by fluorine atoms was determined to be less than 10^{-4} that of chlorine in the 25 to 50 km altitude range.

Table IX

Concentrations of Species and Rate Constants of Reactions Used to Determine ClX Profile
(From data given in Rowland and Molina, 1974)

Altitude, km	25	30	35	40	45	50	55
Temperature	227.1	235.2	251.7	268.2	274.5	274.0	273.6
Concentrations (cm^{-3})							
O_3	4.0(12)	3.8(12)	1.8(12)	5.8(12)	2.0(12)	7.1(12)	2.7(12)
O	6.8(6)	3.2(7)	1.3(8)	3.9(8)	1.2(9)	2.7(9)	4.2(9)
NO	7.5(8)	4.9(8)	5.1(8)	7.0(8)	5.9(8)	3.4(8)	1.8(8)
CH_4	5.4(11)	2.1(11)	7.6(10)	3.1(10)	1.3(10)	6.0(9)	3.0(9)
H_2	6.1(11)	2.6(11)	1.2(11)	4.9(10)	2.1(10)	9.2(9)	3.8(9)
HO_2	2.4(7)	2.8(7)	1.7(7)	8.9(6)	6.3(6)	4.6(6)	3.3(6)
OH	6.0(5)	1.3(6)	3.2(6)	6.7(6)	8.0(6)	6.8(6)	5.2(6)
Rate Constants							
k_7			1.85 x 10^{-11} (temp. independent)				
k_8			5.3 x 10^{-11} (temp. indepedent)				
k_9			1.7 x 10^{-11} (temp. independent)				
k_{12}	1.9(-14)	2.5(-14)	4.1(-14)	6.4(-14)	7.5(-14)	7.4(-14)	7.3(-14)
k_{13}	2.7(-15)	3.8(-15)	7.2(-15)	1.3(-14)	1.5(-14)	1.4(-14)	1.4(-14)
k_{14}			assumed to be 2 x 10^{-11} throughout				
k_{15}	4.7(-13)	4.9(-13)	5.4(-13)	5.9(-13)	6.1(-13)	6.1(-13)	6.1(-13)
Rate of Removal, sec^{-1}							
$k_7(O_3)$	74	70	33	10.7	3.7	1.3	0.50
$k_8(O)$	3.6(-4)	1.7(-3)	9.5(-3)	2.1(-2)	6.3(-2)	1.4(-1)	2.2(-1)
$k_9(NO)$	1.3(-2)	8.3(-3)	8.7(-3)	1.2(-2)	1.0(-2)	5.8(-3)	3.1(-3)
$\Sigma k_x(HX)$ (x=12, 13, 14)	1.2(-2)	8.8(-3)	4.3(-3)	2.8(-3)	1.4(-3)	6.7(-4)	3.4(-4)
k_{17}	2.8(-7)	6.4(-7)	1.7(-6)	4.0(-6)	4.9(-6)	4.1(-6)	3.2(-6)
Cl/ClO	1.8(-4)	1.4(-4)	4.7(-4)	3.1(-3)	2.0(-2)	1.1(-1)	6.5(-1)
HCl/ClO	7.8	1.5	1.2	2.1	5.9	19	49
Fraction of time spent by Cl as:							
HCl	.89	.60	.54	.68	.85	.94	.97
ClO	.11	.40	.46	.32	.16	5.0(-2)	2.0(-2)
Cl	2.0(-5)	5.7(-5)	2.1(-4)	9.8(-4)	2.9(-3)	5.8(-3)	9.0(-3)
Ratio of Cl removal by reaction with O_3 to the combined reactions leading to HCl $[k_7(O_3)/\Sigma k_x(HX)]$:	5.9(3)	1.0(4)	7.7(3)	3.9(3)	2.6(3)	1.9(3)	1.5(3)

Numbers in parentheses are exponents of 10

Rowland and Molina (1974) point out that HF is a reactive gas and its introduction into the stratosphere may have other effects yet undefined. Stolarski and Rundel (1975) note a personal communication from D.D. Davis of the University of Maryland who suggests that the strong hydrogen bonding tendency of HF may lead to large chain molecule formation and eventually to aerosol formation.

Before presenting the current predictions of ozone depletion from fluorocarbons, two aspects of the process should be discussed: the time delay of the effect and the feedback mechanism.

The former aspect takes into account the delay between production and release of the fluorocarbons at ground level and the time when they photodissociate in the stratosphere. Rowland and Molina (1974) have carried out a calculation which demonstrates the time delay. They examined the altitude profiles of F-12 and ClX following a one-year hypothetical introduction of F-12 into the troposphere, with no introduction before or after that year. The results indicate that the F-12 altitude distribution approaches equilibrium after four years, while ClX distribution continues to increase for about ten years. The implication is that the maximum effect of a given year's injection of F-12 occurs approximately a decade later. The time to reach maximum effect will, of course, depend on the diffusion model used.

The feedback mechanism involves the observation that a partial depletion of O_3 at high altitude can result in an increased odd-oxygen production at lower altitudes. With ozone depletion at high altitudes, there will be an increase in the amount of ultraviolet radiation penetrating to the lower altitudes. Some of this radiation (particularly that in the 200-230 nm region) will be absorbed in the lower altitudes by O_2, rather than O_3, resulting in reactions [1] and [2] and an increase in odd-oxygen. It should be pointed out that while the feedback mechanism may result in a shift of the ozone profile to a lower altitude of maximum concentration, the increase in ultraviolet radiation due to ozone depletion will not result in the reformation of an equivalent amount of ozone, even at a lower altitude.

This is because the increased ultraviolet radiation due to ozone reduction is, except for the 200-230 nm region mentioned above, of longer wavelength (less energy) than that which is responsible for the O_2 photolysis which begins the ozone formation process as given in reactions [1] and [2].

Having determined the ClX concentration profile resulting from upward diffusion and photodissociation of fluorocarbons, the effect of the ClX species on local ozone levels can be determined. Predictions of the effects of fluorocarbons on stratospheric ozone are presented in Table X. The differences reflect the various diffusion models, rate constants, and concentrations of minor species used in the calculations. In summary, these predictions indicate that continued F-11 and F-12 production and release to the atmosphere at current rates will lead to an overall ozone depletion of between about 6.5% and 13%, with the full effect occuring sometime in the middle of the 21st century. Crutzen (1974) in one calculation predicts that in addition to an overall ozone depletion of 7%, there will be a slight increase in ozone below 30 km. as a result of the feedback mechanism described above. Of course, where continued expansion of the fluorocarbon industry is assumed, the effect on ozone is more severe and the effect maximizes at an earlier date. Cessation of fluorocarbon production within 5 years would result in an overall depletion of 2% or 3%, maximizing around 1990-1995. Both Rowland and Molina (1974) and Turco and Whitten (1974) conclude that fluorocarbons could currently account for about 1% ozone depletion currently.

The important reactions of chlorine in the stratosphere which affect ozone are summarized by the following diagram:

$$HCl \underset{CH_4[12],\ H_2[13],\ HO_2[14]}{\overset{\cdot OH\ [15]}{\rightleftarrows}} Cl\cdot \underset{O\cdot[8],\ NO[9]}{\overset{O_3\ [7]}{\rightleftarrows}} ClO$$

(The numbers in brackets refer to reactions given earlier in this section.) Those reactions proceeding to the right in this diagram

TABLE X

STRATOSPHERIC OZONE DEPLETION FROM F-11 AND F-12

Reference	Stratospheric O_3 Change	F-11, F-12 Injection Pattern	Atmospheric Diffusion Model		Notes
			Altitude (km)	Eddy Diffusion Coefficient ($cm^2 sec^{-1}$)	
Cicerone et al., 1974	Ozone control passes from NO_x control to ClX control ca. 1985	Exponentially increasing with a doubling time of 3.5 years (current pattern).	15	1.5×10^4	O_3 destruction rates consider only one chlorine atom released per F-11 or F-12 molecule.
			20	2.5×10^3	
			25	7.6×10^3	
	Ozone control passes from NO_x control to ClX control ca. 2000	Exponential increase as above from 1960-1975; then constant at 1975 rate.	30	3.5×10^3	
			35	6.5×10^4	
	Maximum ClX catalyzed O_3 destruction ca. 1990 at a rate comparable to major natural cycles persisting several decades.	Exponential increase as above from 1960-1975; then immediate cessation.	40	1.0×10^5	
			45	1.6×10^5	
			50	2.5×10^5	
Crutzen, 1974	Overall 7% decrease, slight increase below 30 km due to feedback mechanism. Maximum decrease 42% at 40 km. Full effect ca. 2055	Constant at 1973 rate of manufacture.	15-50	10^4	
			50-95	10^4 (exp. 0.13 [z-50]) (z=altitude in km.)	
	Overall 6.5% decrease. Maximum decrease 17% at 40 km. Full effect ca. 2015		15-20	10^4	
			20-30	$10^4 \exp(\frac{z-20}{4.3})$	
			30-50	10^5	
			50-95	$10^5 \exp(\frac{z-50}{10.9})$	
Rowland and Molina, 1974	Overall 13% decrease at steady state (ca. 2050?)	Constant at 1973 rate of manufacture	16-18.8	4×10^3	
			above 18.8	rapid rise to 2×10^6 at 80 km.	

Table X. (cont.)

Reference	Stratospheric O_3 Change	F-11, F-12 Injection Pattern	Atmospheric Diffusion Model Altitude (km)	Eddy Diffusion Coefficient ($cm^2 sec^{-1}$)	Notes
Turco and Whitten, 1974	~6% decrease by 2025, ~10% decrease by 2065.	Constant at 1974 rate of manufacture.	15	~2.5 x 10^4	Infinite tropospheric lifetime.
			20	~7 x 10^3	
			30	~4 x 10^3	
	~3% decrease ca. 2025	As above.	40	~6.5 x 10^3	10 year tropospheric lifetime.
			50	~7 x 10^4	
	~4% decrease ca. 2025	As above.	60	~1.5 x 10^5	30 year tropospheric lifetime.
	>20% decrease by 2025	Beginning at 1974 level, 8.7% increase/year for 20 years, constant thereafter.			Infinite tropospheric lifetime.
	~10% decrease by 2025	As above, 10 year tropospheric lifetime.			10 year tropospheric lifetime.
	>15% decrease by 2025	As above.			30 year tropospheric lifetime.
	~2% maximum decrease by 1995, small residual ozone deficit beyond 2050	Beginning at 1974 level, 8.7% increase for 5 years, then total cessation.			Infinite tropospheric lifetime.
Wofsy *et al*., 1975	~10% by 2064, >13% at steady state.	Constant at 1972 rate of manufacture.	As in Rowland and Molina, 1974 above adjusted upward by factor of 2 between 16 and 20 km.		
	<3% maximum decrease ca. 1990	Beginning at 1972 level, 10% increase/year, with total cessation in 1978.			
	~14% maximum decrease ca. 2000, <5% residual deficit ca. 2064.	As above, with total cessation in 1995.			

Table X. (cont.)

Reference	Stratospheric O_3 Change	F-11, F-12 Injection Pattern	Atmospheric Diffusion Model Altitude (km)	 Eddy Diffusion Coefficient ($cm^2 sec^{-1}$)	Notes
Wolfsy *et al.*, 1975 (cont)	>37% decrease by ca. 2014	Beginning at 1972 level, 10% increase/year, indefinitely			
	~21% maximum decrease ca. 1995, <8% residual deficit ca. 2064	Beginning at 1972 level, 20% increase/year, with total cessation in 1987			
	>37% decrease by 1995.	Beginning at 1972 level, 20% increase/year, indefinitely.			

result in increased ozone depletion; those proceeding to the left decrease the depletion of ozone by chlorine.

Since the ozone depletion prediction given above and in Table X were reported, some of the rate constants of important reactions and concentrations of trace species in the stratosphere have been refined; the effect of these changes have been summarized recently by Rowland (1975). New values of the rates of the reactions shown above (except reaction [14] which has not been refined) agree with those used in the ozone depletion calculations within a factor of two. The rate of reaction [7] has been found to be slower than previously thought, while reaction [12] has been found to be faster. The result of these rate changes is to decrease the effect of chlorine on stratospheric ozone depletion. However, reaction [15] has been found to be faster than originally thought which increases the ozone depletion by chlorine. Further, the concentration of ·OH in the stratosphere as measured recently by Anderson (1975) is somewhat higher than the estimated concentration of ·OH used in the ozone depletion calculations, which also increases the calculated rate of ozone removal by chlorine. The rates of other reactions and concentrations of other species have not changed significantly with new data. The stratospheric concentration of HO_2 and the rate of reaction [14] have not been refined; however, Rowland and Molina (1974) pointed out that this removal path of Cl· is less important than that of reaction [12] (Cl· + CH_4) and may be of negligible importance. Another important reaction yet unrefined is that of ·OH with HO_2 to yield water and O_2. If this reaction is fast, the effect is to decrease the rate of Cl· return through reaction [15] and thus decrease the effect of Cl· on ozone. Most calculations have used the "high" value of the recommended range (between 2×10^{-11} (low) and 2×10^{-10} (high) cm^3-molecule^{-1}-sec^{-1}) and therefore may be underestimating ozone depletion by a factor of two if the "low" value is more accurate.

The net effect of all these corrections (also including the effects of chlorine nitrate as mentioned on page 45) has been basically one of cancellation, and, according to Rowland and Molina (1975), the current predictions of ozone depletion due to the fluorocarbons falls within the range of the initial estimates, that is, 7-13% depletion with continued production of F-11 and F-12 at present rates. Cicerone (1976) currently places the depletion estimate at 8-16% with continued release of F-11 and F-12 at the 1974 rate.

Also, as mentioned earlier, the photodissociation of F-11 and F-12 has been found to be temperature dependent and will proceed more slowly at stratospheric temperature than is indicated in the models where room temperature rates are used. The effect of this modification is not completely clear. One possibility is that the slower release of Cl· from the fluorocarbons would result in a diminished or more delayed effect on ozone concentrations. On the other hand, such a temperature dependence may result in longer lifetimes of the fluorocarbons in the lower stratosphere allowing them to diffuse higher where, with the higher temperature and increased ultraviolet flux and energies, they will dissociate in the more ozone-rich areas of the stratosphere and an increased effect on ozone depletion could occur.

The chlorine-catalyzed ozone destruction models as presented here do not include data on other sources of chlorine to the stratosphere, nor do they consider a natural ClX cycle in the stratosphere, and have been criticized on these accounts. There are only four compounds currently recognized as contributing to the stratospheric chlorine load: F-11, F-12, carbon tetrachloride (CCl_4), and methyl chloride (CH_3Cl). Carbon tetrachloride has been detected in the troposphere at concentrations of 71 ± 7 ppt (Lovelock et al., 1973), 75 ± 8 ppt (Wilkness et al., 1973) and 111-118 ppt (Lovelock, 1974); methyl chloride has been measured in the troposphere at concentrations of 400 ppt (Lovelock, 1975) and 550 ± 50 ppt (Rasmussen, 1975). Methyl chloride is produced naturally in the sea and anthropogenic sources of this compound are insignificant by comparison. Carbon tetrachloride was at one time a widely used industrial compound, but its current uses resulting in release to the atmosphere are probably about 200 million pounds per year (Molina and Rowland, 1974b). Most of the current CCl_4 loading of the atmosphere can be accounted for by man's activity (Singh et al., 1976; Altschuller, 1976). However, because of uncertainties in past production and release factors for carbon tetrachloride, it is not known for certain if the current atmospheric load of carbon tetrachloride is of purely anthropogenic origin or if some is produced naturally.

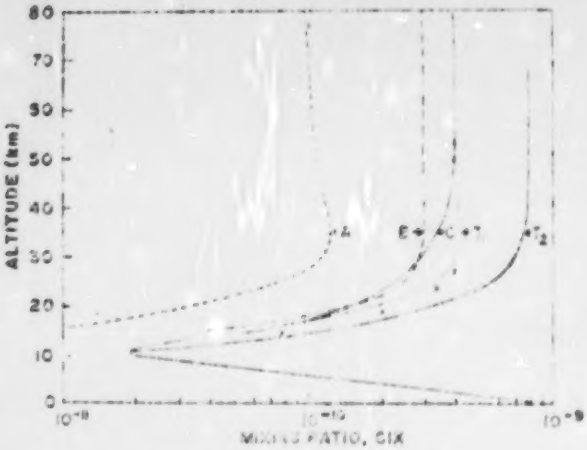
A natural source of chlorine to the stratosphere such as that from methyl chloride and possibly some carbon tetrachloride (as well as the possibility of direct volcanic injection of chloride, industrially released HCl and Cl· from sea spray) would not invalidate the predicted effects of anthropogenically released chlorine compounds (i.e., F-11, F-12, and some carbon tetrachloride) on the stratosphere. The concern is essentially one of changes by man's activities from the natural stratospheric ozone control mechanisms and is analogous to the concern over NO_x emissions from supersonic transports perturbing the natural NO_x cycle of ozone control. The major controllable sources of stratospheric chlorine are F-11 and F-12 and, to a somewhat lesser extent, carbon tetrachloride.

Cicerone et al. (1975) have estimated the stratospheric load of ClX as of late 1974. Although ground level sources of HCl and Cl_2 from such processes as the conversion of sea-salt aerosols to HCl, volcanic emissions, diffusion through the earth's crust, and industrial activities were considered, these were found to be insignificant in their impact on the stratosphere in comparison to F-11, F-12, CCl_4, and CH_3Cl. F-11 and F-12 contributions were calculated in a manner similar to that described previously in this section; for CCl_4 a steady-state profile with photolysis as the only sink was assumed. The steady-state assumption is justifiable since the anthropogenic sources of CCl_4 (at least from the U.S.) have been generally constant for the past two decades, so that the existence of an equilibrium between the troposphere and the stratosphere for this compound seems reasonable. Tropospheric CCl_4 concentrations used were those given above. For CH_3Cl, a steady-state based on above tropospheric measurements was assumed because the sources of this compound seem to be entirely natural. The loss of Cl· from CH_3Cl was considered to be entirely through reaction with ·OH to yield $\cdot CH_2Cl$ (and water), with immediate decomposition of this product by uncertain reaction(s).

The results of these calculations, shown graphically in Figure 4, indicate that if the assumptions of steady-state conditions and chlorine release mechanisms for CH_3Cl and CCl_4 are correct, the current contributions of these compounds to the stratospheric load of ClX species are two to three times greater than that calculated for F-11 and F-12. If the assumption of a current steady-state for CCl_4 is incorrect and anthropogenic sources of this compound are resulting in increasing atmospheric loads, the future stratospheric ClX from CCl_4 will, of course, also increase. However, if it is assumed that CH_3Cl and CCl_4 are presently at steady-state (and, therefore, their contributions to ClX will remain constant in the future), and it is also assumed that F-11 and F-12 will be released at the 1973 rate, then, according to Cicerone et al., the fluorocarbon-derived ClX mixing ratio will be 4×10^{-9} when steady-states are achieved for these compounds in 50-100 years. At that time, F-11 and F-12 would be the major sources of stratospheric ClX.

Cicerone et al. (1975) compared their estimates of ClX to recent measurements of HCl in the lower stratosphere by Lazrus, whose data points are also shown in Figure 4. These measurements show substantial agreement with calculated ClX (recall that ClX is predominantly HCl, particularly at lower stratosphere altitudes) where only F-11, F-12, and CCl_4 are considered as sources. These HCl measurements are lower than would be predicted by ClX estimates which include CH_3Cl as a source. This would imply that one or perhaps all four of the sources are being overestimated, if the HCl measurements are accurate. However, Cicerone et al. point out that the efficiency of HCl collection by Lazrus using impregnated filters may be less than 100% and that improved calibration may increase these HCl values.

Figure 4. ClX MIXING RATIOS AS OF LATE 1974 FROM F-11, F-12, CCl_4, and CH_3Cl AS CALCULATED BY CICERONE ET AL. (1975)



ClX MIXING RATIO FROM:

F-11 and F-12 (A)

CCl_4 (B)

CH_3Cl (C)

F-11, F-12, and CCl_4 (T_1)

F-11, F-12, CCl_4 and CH_3Cl (T_2)

HCl MEASUREMENTS OF LAZRUS INDICATED BY 'X'

Direct proof of the accuracy of the foregoing models of ClX contributions to the stratosphere and resultant ozone depletion can probably be attained only by direct measurement of certain species in the 25 to 50 km altitude ozone-rich area of the stratosphere. Obviously such measurements should include the ClX species. Also, measurement of F-11, F-12, CCl_4, and CH_3Cl would provide useful information on the rate of diffusion and decomposition of these products for comparison to the predicted rates in the models to show which species are in fact contributing to ClX at various altitudes. While methods are available for measuring these latter compounds and only techniques for performing them at these altitudes need be developed, the measurement of the ClX species presents a more difficult problem since no method has been proven successful in measuring stratospheric ClO or Cl·. Lazrus et al. (1975) have developed a method for efficiently collecting stratospheric HCl and particulate Cl (as well as HBr and Br) using balloon-borne alkaline-impregnated filters, although measurements have been carried out only below 30 km. These researchers may have collected some ClO on their filters at 24 to 27.5 km; they are currently studying the efficiency of ClO collection on their filters.

As a final point before discussing the effects of ozone depletion, it should be noted that direct measurement of ozone levels will not be a useful indicator of the validity of these models. Fluctuations in the ozone level are known to occur daily and seasonally and possibly in average readings over longer periods; a cycle synchronous with the 11-year sunspot cycle has been postulated. To measure directly for a true decrease in ozone would require perhaps two decades or more, at which point the proposed effects from F-11 and F-12 would be irreversible and significant. The estimate of a current decrease in ozone of about 1% due to F-11 and F-12 already released is smaller than that which could be established by direct measurement.

VII. EFFECTS OF OZONE DEPLETION

It was stated earlier that the stratospheric ozone layer acts as a filter which shields the earth's surface from solar ultraviolet radiation, particularly from wavelengths below 320 nm. While approximately 90% of the solar ultraviolet radiation of 325 nm incident at the top of the atmosphere reaches sea level, less than 1% of solar ultraviolet radiation of 295 nm reaches the earth's surface. The minimum wavelength observed at sea level is about 288 nm. This filtering out of solar ultraviolet irradiance is due to its absorption by oxygen and ozone in reactions [1] and [3]. Ozone is responsible for absorption of ultraviolet radiation of wavelengths longer than 242 nm, while wavelengths shorter than 180 nm are absorbed almost entirely by oxygen and are not affected by ozone concentration or its altitude distribution. The intermediate wavelengths (especially 200-230 nm) are absorbed by both oxygen and ozone, so that a loss of ozone at high altitudes will permit a deeper penetration of this radiation into the lower stratosphere where, being absorbed by oxygen, it will effect an increase in odd-oxygen. (This is the feedback mechanism mentioned earlier.)

It is, therefore, the ground level intensity of ultraviolet radiation of wavelengths above 242 nm which is expected to increase as a result of ozone depletion. Of most concern, however, are those wavelengths between 280 nm and 320 nm, the UV-B region, with known and suspected biological effects.

The amount of a given wavelength of ultraviolet radiation (of wavelengths longer than 242 nm) which reaches the earth's surface is primarily a function of the intensity of the solar ultraviolet radiation of that wavelength incident at the top of the atmosphere, the ozone absorption coefficient for that wavelength, and the amount of ozone present through which the ultraviolet radiation must pass. The variable in this relationship is the amount of ozone present, and it is noteworthy that the intensity of the ultraviolet radiation reaching the earth's surface is an exponential function with respect to the amount of ozone present. This means that the amount of additional ultraviolet radiation reaching the earth's surface per unit decrease in ozone becomes increasingly greater with each additional unit of ozone depleted. In addition, the intensity of ultraviolet radiation at ground level is influenced by the solar zenith angle, scattering and absorption by particles, droplets, and clouds in the atmosphere, Rayleigh scattering (*i.e.*, the scattering of radiation by particles which are smaller than the wavelength of the radiation), and planetary reflection (Venkateswaran, 1974; Cutchis, 1975). While these factors may influence the amount of ultraviolet radiation reaching earth at a specific time or place, they are independent of the stratospheric ozone concentration. Therefore, the average amount of ultraviolet radiation reaching the earth's surface at a particular place over time is dependent principally upon the amount of ozone through which it passes.

There are two factors to be considered in discussing the ozone depletion problem which were omitted in the model used to develop the quantitative estimates of ozone depletion. These are (a) stratospheric circulation patterns and (b) latitudinal and longitudinal variations in ozone distribution.

The assumption of complete mixing of the fluorocarbons in the troposphere is not inappropriate, since the long tropospheric lifetimes will ensure a tendency toward reducing variations in latitude and longitude. (It could be expected, though, that higher concentrations will occur in the northern hemisphere, where Europe and North America, primary users of the fluorocarbons, lie.) In the stratosphere, however, circulation patterns would favor more rapid upward diffusion at the equator, movement poleward, and downward diffusion near the poles.

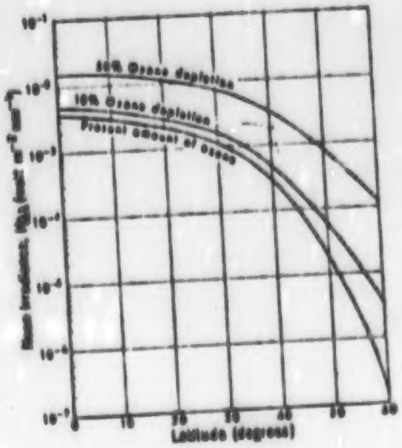
The ozone layer is not uniformly distributed in the stratosphere, but varies with latitude and longitude, and with the day, month, and season. The amount of ozone in a column is least at the equator, increasing significantly at higher latitudes (more so in the northern hemisphere). Ozone occurs generally at higher altitudes in the lower latitudes than in the polar latitudes. At the higher latitudes ozone concentration varies strongly with the season, being highest in spring and lowest in fall.

Photolysis of the fluorocarbons will prevail in regions of highest ultraviolet radiation flux, which are the equatorial regions where the ozone shield is thinnest. Subsequent motions would ultimately carry the ClX species poleward. Ozone depletion may occur more drastically near the equator, with less substantial effects in the higher latitudes.

Cutchis (1974), calculated the effects on solar flux of radiation of wavelength 297.5 nm with hypothetical ozone depletions of 10% and 50%. His results, shown in Figure 5, indicate that relative intensity increases are larger at the higher latitudes. However, the solar flux is much greater at the lower latitudes and, therefore, ozone depletion of equal magnitude at all latitudes results in a much greater absolute increase in ultraviolet flux in the lower latitudes. If, as postulated above, the ozone depletion occurs predominantly at the lower latitudes, the increase in ultraviolet radiation here will be even more dramatic.

From Figure 5 it can be seen that a 10% ozone depletion at all latitudes translates to roughly doubling the solar irradiance in the tropical zones and increases it by an order of magnitude or more at the higher latitudes. Because of the lack of studies on the 280-320 nm region of the ultraviolet spectrum, the exact biological and climatological consequences of such increases are not known. Most studies of ultraviolet radiation have been done with the 254 nm wavelength easily generated by mercury vapor lamps. As a result of the concern for increased ultraviolet flux in the 280-320 nm region, some experiments have been initiated; the preliminary results of these experiments, together with earlier photobiological data, indicate the following, according to Urbach (1974):

Figure 5. Noon direct irradiance at 297.5 nm plotted against latitude for the Northern Hemisphere in the spring. (Cutchis, 1974) (Copyright 1974 by the American Association for the Advancement of Science, reprinted with permission.)



(1) Most of the biological effects of radiation in the 280-320 nm region are decidedly detrimental.

(2) Most organisms have developed the ability to avoid excessive ultraviolet radiation, either by behavioral patterns, or by protective coverings, such as fur, leathers, cuticular wax, etc. The capacity for avoidance of excessive radiation is limited in most organisms, and many currently exist near a threshold where an increase in exposure to ultraviolet radiation would be detrimental.

The issue which has received the most attention as a result of the ozone depletion potential is the effects of increased ultraviolet radiation on humans. Among the effects attributable to ultraviolet radiation are erythema solare, commonly referred to as sunburn; skin aging, characterized by wrinkling, blood vessel dilation, atrophy, etc.; and skin cancer.

The hypothesis of increased skin cancer due to increased ultraviolet radiation is based on extensive experimental results of effects on laboratory animals and on limited epidemiological studies. Some of the arguments, reviewed by Urbach (1974), which indicate a relationship between human skin cancer and ultraviolet radiation are:

(a) Superficial skin cancers occur most often on parts of the body habitually exposed to sunlight;

(b) there is a lower rate of skin cancer among pigmented races who sunburn much less readily than white-skinned peoples;

(c) there is a higher rate of skin cancer in Caucasians who work predominantly outdoors than in those who work indoors;

(d) genetic diseases (albinism, xeroderma pigmentosum) which result in greater sensitivity to the dermal effects of solar ultraviolet radiation are associated with marked increases and early skin-cancer development.

Although some estimates have been made of the increase in the number of skin cancers per year as a result of ozone depletion, such estimates are subject to great, and currently unmeasurable, uncertainty. Early estimates indicated a 20% increase in human skin cancer for a 10% reduction in ozone. It has more recently been estimated that a 10% ozone reduction could lead to 25-35% increases in human skin cancer. The uncertainty in such estimates notwithstanding, the evidence does lead to the qualitative conclusion than an increase in ground-level ultraviolet radiation will result in some increase in the incidence of human skin cancer.

Little is known concerning the effects of increased UV-B on domestic and wild animals, although some observations were made by the Federal Task Force on Inadvertent Modification of the Stratosphere (IMOS, 1975). It has been assumed that the outer covering of most animals (hair, feathers, shells, normal pigments, etc.) provide protection from the harmful effects of UV-B. It is not known to what degree these coverings will provide protection from the effects of increased levels of ultraviolet radiation. Wild animals are generally nocturnal in habit, and also tend to remain in the shade provided by forests during daylight activities. Because of this behavior, increased ultraviolet radiation may have little effect on these animals in a practical sense. Certain domestic animals, which may not have protective shade, are probably at greater risk to the harmful effects of increased UV-B. Skin cancer is known to occur in cattle, goats, sheep, and horses, and is found predominantly in parts of the body where the amount of the pigment melanin is least, such as the eyelids, genitals, and skin near brand marks. The incidence of "cancer eye" which, according to IMOS, accounts for more than 90% of all slaughterhouse condemnations has a higher incidence in white-faced Hereford cattle than in the more darkly colored species. In addition, geographical locations with greater exposure to natural sunlight are associated with higher incidence of cancer eye in these white-faced cattle. Ultraviolet radiation may increase the effects of the bacteria-induced disease of cattle known as pink eye, and may also increase the number of cattle affected. Adverse effects from increased UV-B may also occur in cattle exposed to photosensitizing materials, which are known to occur in a variety of grasses and weeds. Microorganisms and drugs (such as phenothiazine, commonly used to treat parasitic infections) are photosensitizers.

There are practically no data available on the effects of increased UV-B on insects. The National Academy of Sciences (1975) notes that the mortality of caged insect larvae increases with supplemental ultraviolet radiation, but, because these larvae keep sheltered from the sun in nature, the significance of this finding is difficult to determine. Some qualitative observations regarding the interactions of insects with ultraviolet light have also been made. For example, insect eyes are capable of detecting ultraviolet radiation; in fact, insects are guided in feeding and pollinating by ultraviolet reflectance patterns on flowers. In some butterflies and perhaps other insects, mate selection involves visual cues that include ultraviolet light reflectance patterns. How increased ultraviolet radiation due to ozone reduction would affect these mechanisms is not known at this time.

In addition, little is known about the possible effects of ultraviolet radiation in the UV-B range on plants. A few studies cited by the National Academy of Sciences (1975) designed to show the effects of increased ultraviolet radiation corresponding to a 50% reduction in ozone showed significant growth reduction in peas (two varieties), cabbage, collard, and corn. Plant growth was inhibited by 20 to 50% in greenhouse and growth chamber experiments, while field experiments showed smaller, but statistically significant decreases for some plants. The chlorophyll content of beans and cabbage exposed to supplemental UV-B in growth chambers showed a 10 to 30% decline. UV-B-exposed collards showed reduction in photosynthetic capacity. Soybeans exposed to supplemental UV-B in field experiments showed degenerative changes in the structure of some cells. In spiderwort exposed to supplemental UV-B under field conditions, an increase in harmful mutations, determined by abnormal or missing stamen hairs was observed. With regard to plants in general, seedlings are more sensitive to the effects of ultraviolet radiation than are mature plants, and single-celled algae are many times more sensitive.

Because of its absorption of ultraviolet radiation, the stratospheric ozone layer also serves to warm the upper stratosphere. Depletion of ozone or shifting to lower altitudes may affect the temperature structure of the stratosphere which may in turn alter the tropospheric climate. Possible alterations such as temperature distribution and rainfall patterns may affect crop yields, timber production, and certain aquatic and terrestial ecosystems. In studying the effects of stratospheric aircraft on ozone, the National Academy of Sciences (1975) stated that "as far as climatic change and agricultural effects are concerned, no clear-cut statement can be made concerning expected changes in temperature and rainfall. Nevertheless, a global change in temperature of a few tenths of a degree and an associated change in rainfall are not ruled out. Local changes may be larger, and the economic, social, and political effects of such changes could be substantial".

Except perhaps for the increases in skin cancer, there is insufficient information currently available to quantify the biological and climatological effects of partial ozone depletion.

Research is currently being conducted to test the theory of fluorocarbon-catalyzed ozone depletion. Under the coordination of the Interdepartmental Committee for Atmospheric Sciences (ICAS), studies are being performed by the National Aeronautics and Space Administration, the Energy Research and Development Administration, the Environmental Protection Agency, the National Science Foundation, and the Departments of Commerce, Defense, and Transportation. Additional research is being sponsored by 19 fluorocarbon manufacturers under the coordination of the Manufacturing Chemists Association. The principle areas of investigation include stratospheric measurements of F-11, F-12, aand other chlorine species, measurement of other important species in stratosphere (especially the ·OH and HO_2 radicals), and measurements of chemical reaction rates. Studies are also being made to determine what substitutes for fluorocarbons are available and the economic impact of possible regulatory actions.

Although not involving ozone depletion, another effect of fluorocarbons in the atmosphere that might result in climatological changes was reported recently by Ramanthan (1975). The presence of these compounds and other chlorocarbons in the troposphere may enhance the atmospheric "greenhouse effect". The "greenhouse effect" (a term which Fleagle and Businger (1975) suggest be replaced by "atmospheric effect" because of fallacies in the analogy) results from the absorption of infrared radiation emitted by the earth's surface by compounds in the troposphere resulting in an increase in the temperature of the atmosphere. In examining the infrared absorption bands of F-11 and F-12, Ramanthan concludes that tropospheric levels of 2 ppb of these compounds (expected to be reached by the year 2000 if present use patterns are maintained) will result in an increase in the mean global surface temperature of 0.9°C, which is above that considered sufficient to substantially alter some climatic variables, such as rainfall and ice cover, in at least certain parts of the globe. The results of Ramanthan may, according to Machta (1975), be somewhat overstated since the overlap in infrared absorption spectra of the fluorocarbons with that of water was not included in the model.

VIII. BIOLOGICAL PROPERTIES OF FLUOROCARBONS

A. Absorption and Elimination

1. Inhalation

Because of the physical properties and uses of the fluorocarbons under review here, inhalation is the most likely route of entry into terrestrial vertebrates. Several studies have been reported for both standard laboratory animals and man on the absorption and elimination of inhaled fluorocarbons during and after exposure. The method of exposure may be via inhalation of a known concentration in ambient air (usually expressed as percent by volume) or via direct inhalation from a bronchodilator-type nebulizer (usually expressed as milligrams of fluorocarbon inhaled). The absorption/elimination pattern of fluorocarbons may be determined by measurement of blood levels or by measurement of fluorocarbon in expired air. It must be recognized that parameters other than dose and method of exposure affect the amount and rate of absorption and elimination of an inhaled gas. Blood levels attained under similar exposure conditions will vary with different species, different individuals in the species, and a given individual at different activity levels. Absorption and elimination are dynamic processes involving equilibria between the ambient air and blood, between the blood and body tissues, and between the various body tissues themselves. Fluorocarbon blood levels as a function of time during and following exposure are instructive of both the absorption/elimination pattern and the equilibrium state.

Howard *et al*. (1974) have discussed the fluorocarbon absorption/elimination literature in considerable detail. The available data on blood levels of fluorocarbons in animals exposed to them in ambient air are presented in Table A-I (Appendix A). Figures A-1 - A-3, from Clark and Tinston (1972a) are typical of the absorption and elimination patterns of fluorocarbons inspired from ambient air.

Absorption of inhaled fluorocarbons follows a biphasic pattern, where a rapid initial increase in blood levels is followed by a slower approach to a maximum concentration, at which point an apparent equilibrium is reached between blood and ambient air. Azar *et al*. (1973), Allen and Hanburys (1971) and others have measured arterial and venous blood levels during this period of apparent equilibrium. Their data show that arterial concentrations exceed venous concentrations during the equilibrium period, indicating that fluorocarbon is being removed from the blood by tissue absorption, and, therefore, true equilibrium is not reached until the venous-arterial levels are equal and constant. When exposure is terminated, a similar biphasic pattern of elimination is observed, where a rapid initial fall in blood levels is followed by a slower decline to undetectable levels (0.005 µg/ml for F-11; 0.15 µg/ml for F-12, Azar *et al*., 1973). During the elimination phase after exposure is terminated, the venous levels exceed arterial levels, indicating the removal of fluorocarbons from tissue.

Absorption/elimination of fluorocarbons administered in single or limited dosages as from a bronchodilator-type nebulizer shows a similar pattern of rapid initial rise in blood levels, followed by rapid, then much slower elimination.

The relative order of absorption appears to be F-11 > F-113 > F-12 > F-114 (Shargel and Koss, 1972), with limited data indicating that F-13B1 is absorbed to about the same degree as F-12 (Griffin *et al*., 1972). Shargel and Koss (1972) have also shown that there is no indication that the presence of one fluorocarbon influences the relative degree of absorption of another fluorocarbon.

2. Other Routes of Entry

Although inhalation is the route of entry of most concern for the fluorocarbons under review here, other routes of entry have received some study. In a long-term feeding study of F-12 to rats and dogs, Sherman (1974) found tissue uptake indicating that some absorption does occur across the gastrointestinal tract.

Dermal absorption of F-113 has been tested in man (DuPont, 1968). The hands and arms of two individuals were immersed in F-113 for 30 minutes and portions of the scalp were exposed to F-113 for 15 minutes. Fluorocarbon uptake was measured as F-113 in expired air. Time to maximum concentration is measured from termination of exposure. The maximum concentrations noted in exposure of the hands and forearms were 9.6 ppm after 11.5 minutes for one individual and 1.7 ppm after 23 minutes for the other. The scalp, perhaps because of its greater vascularity, seems somewhat more absorbent with one individual reaching a maximum fluorocarbon concentration of 12.7 ppm in 20.5 minutes and the other reaching 7.4 ppm after 18.5 minutes. After 90 minutes, F-113 concentrations were below 0.5 ppm in all subjects. In the subject showing 1.7 ppm in the hand and forearm exposure, however, a trace amount of about 0.1 ppm was detected 18 hours after exposure.

Regardless of the route of entry, elimination of fluorocarbons seems to be solely through the respiratory tract. Matsumato _et al_. (1968) administered a mixture of F-12 and F-114 (30/70, v/v) to dogs intravenously, intraperitoneally, intramuscularly, or sprayed directly onto the liver and kidney. Elimination occurred through expired air, with no fluorocarbon detected in the urine or feces.

In summary, the available data on fluorocarbon absorption and elimination indicate that fluorocarbons are absorbed across the alveolar membrane, gastrointestinal tract and skin. Inhaled fluorocarbons are readily taken up by the blood and, with continued exposure in ambient air, an equilibrium state is reached between the air, blood and tissues (indicated by equal concentrations in arterial and venous blood). Fluorocarbons absorbed by any route are eliminated through the expired air, with the biphasic pattern of rapid initial elimination followed by a slower decline as described previously.

B. Transport and Distribution

It is apparent from the preceding information on absorption and elimination that the fluorocarbons are transported by the blood and that some tissue storage occurs during continuous exposure, as evidenced by higher levels in arterial than in venous blood during exposure, with a reversal after exposure is terminated and the compounds are being eliminated.

Data from Allen and Hanburys, Ltd. (1971) show that subsequent to a five-minute exposure in ambient air to rats, F-11 and F-12 are concentrated from the blood to the greatest extent in the adrenals followed by the fat, then the heart. Brain and liver levels were apparently not measured. Carter *et al*. (1970) exposed rats to F-113 for 7 and 14 days and found F-113 primarily in the fat, with significant levels in the brain, liver, and heart. Van Stee and Back (1971) found that concentrations of F-13B1 during and after five-minute exposures of rats were significantly higher in the brain than in the heart. While there is temporary storage in those tissues of high lipid content during continuous exposure, elimination after termination of exposure is rapid and there is no indication that the fluorocarbons are accumulated in any tissue. The ambient air concentrations to which the test animals were exposed in the above studies were in the range of about 0.2% to 1.0%, which are about six orders of magnitude higher than the 100-600 ppt found in urban air.

C. Biochemical Interactions

Griffin *et al*. (1972) found that inhaled F-12 or F-13B1 had no effects on oxidation or phosphorylation in isolated mitochondria from the liver, lung, brain, heart, and kidney of rats, nor in liver and heart mitochondria exposed to these compounds *in vitro*.

Paulet *et al*. (1975) studied the metabolic effects of inhaled F-11 and F-12 in the rat, rabbit, and dog. With a 5% concentration of F-11, given either as a single twenty-minute exposure or for two one-hour periods daily for fifteen days, there was an observed decrease in oxygen uptake, slight hyperglycemia and hyperlactacidemia, a slowing of hepatic glycogen secretion, an increase in the respiratory quotient, a decrease in blood urea, and a slight increase in free fatty acids. These effects, which indicate a slowing down of cellular oxidation, were not observed with exposure to 2.5% F-11, nor with F-12 at single exposure to 20% or repeated exposures to 5%.

D. Metabolism

Of the fluorocarbons under review, only F-11, F-12, and halothane are topics of published reports on metabolism. Cox et al. (1972a) have attempted to demonstrate possible reductive dehalogenation of F-11 in two ways. First, reasoning that the primary products of dehalogenation would be F-21 ($CHCl_2F$) and F-112 ($C_2Cl_4F_2$), they incubated F-11 in microsomal preparations from rats and chickens and from rats, mice, guinea pigs, and hamsters pretreated with phenobarbital to stimulate metabolism. No F-21 was detected. Secondly, as an index of free radical formation, they measured the effect of F-11 on lipid peroxidation. No evidence of free radical formation was found.

Blake and Mergner (1974) have studied the metabolism of inhaled F-11 and F-12 using carbon-14 labelled compounds in anaesthetized beagles. The radiolabelled impurities in F-11 (89.6% pure) were 9% $^{14}CCl_4$ and 1.4% $^{14}CHCl_3$. The radiolabelled impurities in F-12 (96.0% pure) were $^{14}CF_3Cl$ and/or $^{14}CF_4$. In both of the fluorocarbon preparations, less than 0.1% of the radioactivity appeared as $^{14}CO_2$. Exposures of F-11 ranged from concentrations of 0.19% to 0.55% for periods of six to twenty minutes. Exposures of F-12 ranged from concentrations of 0.82% to 11.8% over the same period. The exhaled air was assayed for $^{14}CO_2$ as the index of metabolism; non-volatile urinary and tissue radioactivity were also measured, but this was not identified with specific compounds. After removing the $^{14}CO_2$, exhaled air was combusted in an oxygen/hydrogen flame which, according to the authors, converted the unmetabolized exhaled [^{14}C]-fluorocarbon to $^{14}CO_2$ for assay. The experiment suffered from this procedure since it precluded the identification of volatile metabolites in the exhaled air other than $^{14}CO_2$. In both the F-11 and F-12 studies, the total recovery of exhaled $^{14}CO_2$ and non-volatile urinary and tissue radioactivity was about 1% of the administered dose. Because of the radioactive impurities in the F-11 sample (carbon tetrachloride and trichloromethane which are both known to be metabolized in animals), the F-11 study gives no firm evidence for fluorocarbon metabolism. However, in the F-12 study, all of the administered radioactivity was in the form of fluorocarbons: 96% F-12 and 4% F-13 and/or F-14. According to the current view of fluorocarbon biological activity, increasing fluorination leads to increasing stability. Consequently, of these three compounds, F-12 would probably be the most readily metabolized. The F-12 study thus seems to indicate that, at most, only about 1% of F-12 - and/or F-13 and F-14 - are metabolized after relatively brief exposures.

Eddy and Griffith (1971) observed metabolism in rats following oral administration of F-12 labelled with carbon-14. About 2% of the total dose was exhaled as CO_2 and about 0.5% was excreted in the urine. By thirty hours after administration, the fluorocarbon and its metabolites were no longer present in the body.

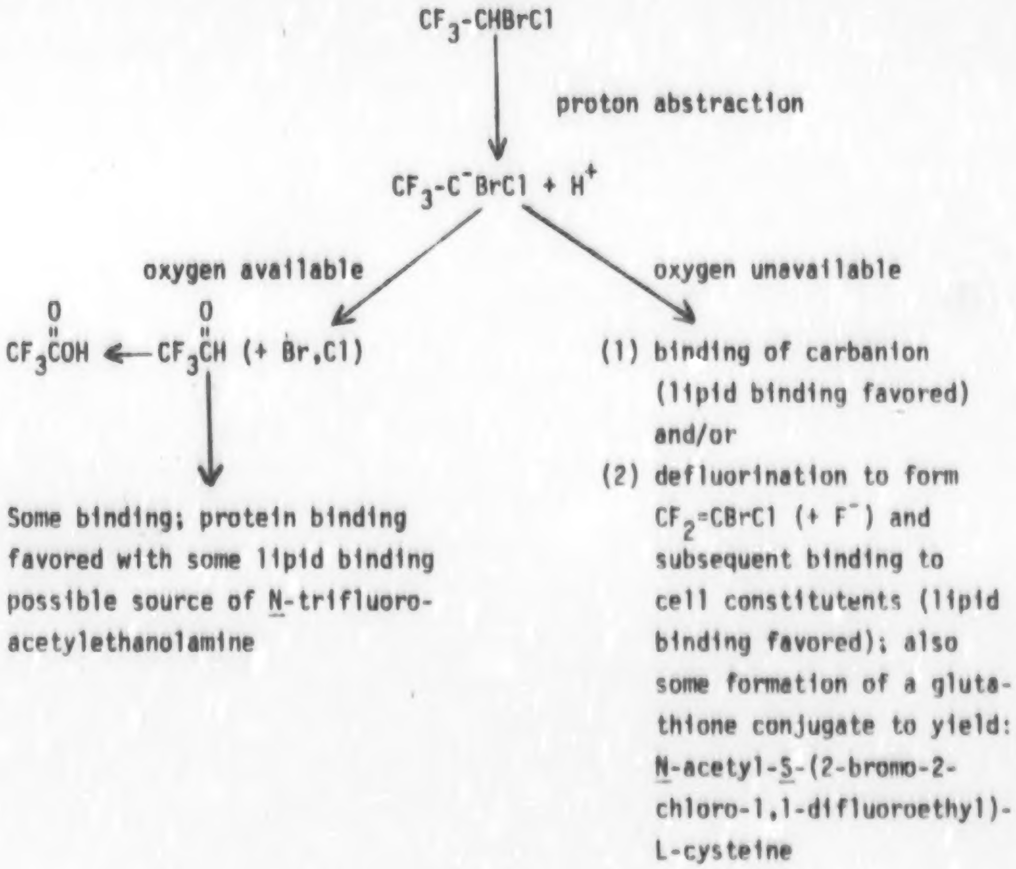
Blake and Mergner (1974) have indicated that the apparent resistance of F-11 and F-12 to biotransformation may be more a function of their rapid elimination than their general stability. Over long periods of exposure, the fluorocarbons will not only be in equilibrium with tissue for long periods, but will also be more likely to access "deep" tissue compartments not reached when exposure is terminated and elimination occurs.

Because the surgical use of the volatile anesthetic halothane (CF_3-CHBrCl) has been associated with occasional incidents of liver toxicity, the metabolism of this compound has been investigated. The precise mechanism of halothane metabolism has not yet been established, but several metabolites have been identified. The primary metabolic products are trifluoroacetic acid (CF_3-COOH), inorganic bromide and products are trifluoroacetic acid (CF_3-COOH), inorganic bromide and inorganic chloride. Based on the amount of trifluoroacetic acid and inorganic bromide recovered from the urine of humans, approximately 20% of an administered dose of halothane is metabolized in humans (Rehder *et al.*, 1967; Stier *et al.*, 1964). More recently, *N*-trifluoroacetylethanolamine and *N*-acetyl-*S*-(2-bromo-2-chloro-1,1-difluoroethyl)-L-cysteine have also been identified as human urinary metabolites (Cohen, 1971; Cohen *et al.*, 1975). This latter compound, an apparent glutathione conjugate, indicates that some halothane undergoes defluorination, which was previously thought not to occur. Under conditions favoring defluorination (described below), inorganic fluoride is also a halothane metabolite. In addition to these excretable metabolites, it is also known that some halothane is transformed to reactive products which bind covalently to cellular phospholipids and proteins (Van Dyke and Gandolfi, 1974; Van Dyke and Wood, 1975; Werner and Uehleke, 1974; Uehleke *et al.*, 1973).

These bound metabolites are of particular interest with respect to the liver toxicity of halothane following clinical anesthesia because (a) trifluoroacetic acid is not toxic at the concentration at which it appears and (b) the liver toxicity of carbon tetrachloride, chloroform, acetaminophen, and bromobenzene correlates with bound metabolites (Van Dyke, 1973; Van Dyke and Wood, 1975). Both *in vitro* and *in vivo* studies have shown that one of the major factors influencing the metabolism of halothane and the formation of bound metabolites is oxygen availability. Using hepatic microsome preparations from rats and ^{14}C-labelled halothane, it has been observed that under aerobic conditions the primary metabolites are trifluoroacetic acid and chloride (bromide not measured), with some binding of ^{14}C to phospholipid and protein and with only trace amounts of inorganic fluoride produced. Under anaerobic conditions (N_2 atmosphere), only a trace amount of trifluoroacetic acid is produced and there is a decrease in the inorganic chloride production, while the amount of bound metabolites and the level of inorganic fluoride are markedly increased. However, from the molar amounts of fluoride observed (assuming that only one fluorine is removed per halothane equivalent bound), it was evident that metabolites other than the defluorinated one(s) were also involved in the binding (Van Dyke and Gandolfi, 1976).

Widger *et al*. (1976) demonstrated *in vivo* with rats that halothane metabolism is influenced by oxygen availability. In their study, rats receiving halothane with an adequate oxygen supply (25-60%) showed a lipid/protein ratio for bound metabolites of 0.76 ± 0.14 with no significant increase in fluoride levels. Under hypoxic conditions (7-14%), there were large increases in the amount of fluoride produced and, relative to the non-hypoxic group, approximately twice the amount of total bound metabolites, with a threefold increase in lipid binding, a decrease in protein binding, and a lipid/protein binding ratio of 3.24 ± 1.29.

These studies indicate that halothane can undergo both oxidative and non-oxidative metabolism. Van Dyke and Gandolfi (1976) suggest that the initial step in the metabolism of halothane is the abstraction of a proton to form a carbanion which, oxygen, can bind to cell constitutents directly and can also undergo defluorination to form additional bound metabolites. Where oxygen is available, the carbanion is oxidized to trifluoroacetic acid, bromide, and chloride. Although it has yet to be isolated experimentally, trifluoroacetaldehyde has been proposed as an intermediate in the oxidative pathway of halothane metabolism to trifluoroacetic acid. Trifluoroacetaldehyde could be involved in the binding observed with oxidative metabolism of halothane and in the formation of the trifluoroethanolamine metabolite which has been identified. The metabolism of halothane suggested by the currently available data is summarized schematically below:



Some binding; protein binding favored with some lipid binding possible source of N-trifluoroacetylethanolamine

(1) binding of carbanion (lipid binding favored) and/or

(2) defluorination to form $CF_2=CBrCl$ (+ F^-) and subsequent binding to cell constitutents (lipid binding favored); also some formation of a glutathione conjugate to yield: N-acetyl-S-(2-bromo-2-chloro-1,1-difluoroethyl)-L-cysteine

Although halothane contains a hydrogen atom that is lost as the initial step in its metabolism, there is evidence that perhalogenated materials, notably carbon tetrachloride and the fluorocarbons F-11 and F-12, also form metabolites which can bind to cell constituents. Uehleke and Werner (1975) have demonstrated in vitro using anaerobic suspensions of liver microsomes from rabbits (pretreated with phenobarbital to stimulate metabolism) that F-11 binds irreversibly to both endoplasmic phospholipids and proteins. Cox et al. (1972b) have obtained spectral evidence which indicates that F-11 binds to the phospholipid environment of cytochrome P-450 from rat-liver microsomal preparations, and also to another site apparently similar to the CO-binding site. Further, in the in vivo study of Blake and Mergner

(1974) discussed previously, there was some binding of radioactivity to tissue which could have been due to F-11 and F-12, but, owing to the impurities in the radiolabelled materials, this cannot be stated as conclusive.

If the development of liver toxicity from halothane is associated with the formation of bound metabolites, as appears to be the case with carbon tetrachloride and other substances mentioned previously, these metabolism studies could explain the "occasionality" of the toxic response. The formation of bound halothane metabolites, particularly to lipids, is clearly favored by an inadequate oxygen supply to the liver, a circumstance which could exist during certain surgical procedures due to the physiologic condition of the patient or to some degree of hypoxia during anesthesia. It is also conceivable that a buildup of bound metabolites could occur from repeated exposure to halothane, even when there is no hypoxia, resulting from either the binding of an intermediate (trifluoroacetaldehyde) in the oxidative pathway leading to trifluoroacetic acid and/or from binding of metabolites from the non-oxidative pathway which may also occur to some extent even under conditions of adequate oxygen supply.

The evidence available on the formation of bound metabolites from halothane, and the scant, but significant, data showing that F-11 and F-12 may also be metabolized to substances which bind to cell constituents point to the need for further attention to fluorocarbon metabolism. The presence of a hydrogen atom, as in halothane, may be an important factor in the extent to which the fluorocarbons are metabolized. Because the fluorocarbons which have been proposed as replacements for F-11 and F-12 all contain hydrogen atoms (namely, F-133a (CF_3CHCl_2), F-142b ($CClF_2$-CH_3), F-152a (CHF_2-CH_3), F-22 ($CHClF_2$), and the 120 (monohydrogen ethane) series of fluorocarbons), these materials clearly need to be examined for metabolism to substances which bind to lipids and protein. The perhalogenated fluorocarbons may also form metabolites which bind to lipids and proteins and, although the data on F-11 and F-12 seem to indicate that this does not occur to a significant extent with acute exposures to these two compounds, the extent to which bound metabolites might build up from long-term exposure is worthy of further study. The other commercially important fluorocarbons, such as F-113, F-114, and F-115, for which no metabolism data were found, should also be examined for the formation of bound metabolites.

IX. HUMAN TOXICITY STUDIES

Much of the information available on the toxicity of the fluorocarbons to humans involves the intentional or unintentional misuse of fluorocarbon-containing products involving inhalation of high concentrations of the compounds. Of particular note is the experience of abusive inhalation of fluorocarbon propellants by young people attempting to reach an intoxicated state. Bass (1970) has associated 57 deaths occurring between 1960 and 1969 with inhalation of fluorocarbon propellants. Kilen and Harris (1972) have reported that over 140 such cases of fatal intoxication from abusive inhalation of aerosol propellants have been documented. The method of inhalation involves spraying the aerosol product into a bag, placing the bag over the nose and mouth, or over the entire head, and inhaling the contents deeply. While asphyxia is a potential hazard, the cause of death is most probably cardiac arrhythmia, possibly aggravated by elevated levels of catecholamines due to stress and/or an increase in blood carbon dioxide (Bass, 1970). The cardiac effects of fluorocarbons are described in Section XI.

While similar concern exists over the role of fluorocarbons in deaths of asthmatics using fluorocarbon propelled bronchiodilator drugs (Taylor and Harris, 1970b; Archer, 1973), there is no unequivocal evidence that the fluorocarbons are directly responsible for fatalities under these circumstances (Silverglade, 1971; Aviado, 1975c).

Except for the hazards of the fluorocarbon anesthetic halothane to operating room personnel (discussed later in this section), there has been only one report of a specific adverse effect resulting from occupational exposure to the fluorocarbons. Speizer et al. (1975) found that persons working in the pathology department of a Boston hospital who used a fluorocarbon aerosol product (usually F-22, though some F-12 was also used) in preparing frozen tissue sections had a 3.6 relative risk of heart palpitations compared to non-exposed employees in the same department and in a different department (radiology). A dose-response relation was noted between maximum number of frozen sections prepared weekly and episodes of palpitation. Palpitations were reported by 3 of 6 persons (50%) preparing 10 or more frozen slides per week; 5 of 11 (46%) preparing 5-9 frozen slides per week; and 5 of 14 (36%) preparing less than 5 frozen slides per week. The incidence of palpitation among non-exposed persons was 20 of 87 (23%). In an attempt to estimate F-22 exposure under work conditions, air from the breathing zone was monitored during the slide preparation procedure. With two 10-second blasts of the aerosol cannister (100% F-22), the average exposure of F-22 over the two-minute period was 300 ppm.

Imbus and Adkins (1972) found no signs of toxicity in a group of 50 workers exposed to F-113 (being used for degreasing in "clean rooms" of Kennedy Space Center) for up to 4.5 years (mean 2.77 years) at concentrations of 46 to 4700 ppm (mean 669 ppm; median 435 ppm). Blood levels of F-113 were not measured.

In a study of fluorocarbon blood levels in 20 women using fluorocarbon-propelled aerosol products (average of 21.6 g of fluorocarbon propellants per woman per day), Marier et al. (1973) found no measurable blood levels of fluorocarbons. The limits of detection were 0.004 ppm for F-11, 0.1 ppm for F-12, and 4 ppm for F-114. Marier et al. (1973) were also unable to detect any abnormalities in various hematological and respiratory parameters, nor in the overall health of the subjects. The women were exposed to the fluorocarbons under normal use circumstances for the aerosol products, but the amounts of fluorocarbon to which they were exposed were estimated to be greater than nine times that of normal use.

Exposure to humans under experimental conditions has been thus far limited to three of the most common fluorocarbons: F-12, F-113, and F-13B1.

Fluorocarbon-12 has been tested using human subjects by both Kehoe (1943) and Azar et al. (1972). Kehoe (1943) exposed one subject to concentrations of 4%, 6%, 7%, and 11% for periods of 80, 80, 35, and 11 minutes, respectively. A second subject was exposed to 4% for

14 minutes immediately followed by 2% for 66 minutes. At 4% F-12, the subjects experienced a tingling sensation, humming in the ears, and apprehension. Electroencephalographic changes were noted as well as slurred speech and decreased performance in psychological tests. In the one subject exposed to higher concentrations, these signs and symptoms became more pronounced with increases in concentration. An exposure of 11% caused a significant degree of cardiac arrhythmia followed by a decrease in consciousness with amnesia after ten minutes. At concentrations of 1% F-12 for 150 minutes, Azar et al. (1972) noted a 7% decrease in psychomotor test scores and no effects at 0.1% concentration over the same period.

Fluorocarbon-113 has been tested on human subjects by Stopps and McLaughlin (1967) and Reinhardt et al. (1971). Psychomotor performance was evaluated with exposures to 0.15%, 0.25%, 0.35%, and 0.45% F-113 for 165 minutes (Stopps and McLaughlin, 1967). At the lowest level, no effect was noted. At 0.25% there was difficulty in concentrating and some decrease in test scores. These effects were more pronounced at 0.35% F-113. At 0.45% F-113, performance at various tasks was decreased by between 10% and 30%. These decreases coincided with sensations of "heaviness" in the head, drowsiness, and a slight loss of orientation after shaking the head from left to right. Reinhardt et al. (1971) exposed human subjects to concentrations of 0.1% and 0.05% F-113 for 130-minute periods in the morning and afternoon on five days. No decreases in psychomotor ability were noted. No abnormal findings were noted during post-exposure physical examination, hematologic and blood chemistry tests (conducted three days after final exposure) and steady-state measurements of diffusing capacity of lungs and fractional uptake of carbon monoxide.

Fluorocarbon-13B1 exposures to human test subjects have been summarized by Reinhardt and Reinke (1972). Concentrations of 1%, 3%, and 5% F-13B1 for periods of three to three and a half minutes had no effect on electrocardiograms or response times in three subjects.

Concentrations of 7% and 10% over the same period, however, did result in slight lessening of equilibrium and increase in response time (Reinhardt and Stopps, 1966).

Similar results were obtained at Hine Laboratories (1968) over longer durations. Concentrations of 5% F-13B1 for 20-25 minutes caused a minimal decrease in psychomotor performance while concentrations of 10% caused a more pronounced decrease in ten subjects. Drowsiness and an increased sense of well-being were also noted. Graded concentrations of 5-17% F-13B1 over periods of 15-20 minutes resulted in central nervous system effects ranging from tingling to a feeling of impending unconsciousness (14% F-13B1) in nine of ten subjects, with the remaining subject reporting no effects at concentrations up to 15.7%. Cardiac effects were noted in three of ten subjects. Effects in two subjects at 8.2-15.7% F-13B1 were primarily T-wave alterations (depression and flattening), with increased sinus arrhythmias occurring in one of these subjects. The third subject showing cardiac effects exhibited T-wave flattening after an inital exposure to 16.9% F-13B1, but 36 hours later, after a five-minute exposure to 14% F-13B1, developed cardiac arrhythmias including T-wave flattening, extrasystoles forming bigeminy, A-V dissociation, and multifocal premature beats. Clark (1970) has also noted T-wave depression and tachycardia along with loss of equilibrium and paresthesia in all subjects after less than a one-minute exposure to 12% and 15% F-13B1. T-wave depression was noted at 10% exposures for one minute in two subjects, along with slight dizziness and paresthesia. Three-minute exposures to 9% and 6% resulted in similar central nervous system effects and tachycardia.

In addition to these studies, Call (1973) exposed eight subjects to concentrations of 4% and 7% F-13B1 for three minutes in a hypobaric chamber maintained at 760 mm Hg, 632 mm Hg (equivalent to 5,000 feet), and 380 mm Hg (18,000 feet). Although no cardiac effects were noted in any of these exposures, reaction times were increased from about 550 milliseconds to about 600 milliseconds at both concentrations and at all altitudes.

There have been two reports dealing with the effects of aerosol product usage on respiratory parameters in humans. Although the fluorocarbons are the most commonly used propellants and tend to be a common denominator for many aerosol products, it must be emphasized that, in these studies, the effects observed are not necessarily attributable to the fluorocarbons. Not all products contain fluorocarbons propellants and even those which do also contain diverse other ingredients to which the user is exposed.

Good et al. (1975) report an excess of moderate and marked atypical metaplastic cells in sputum samples among frequent users of aerosol products. None of the frequent users in this study complained of symptoms of respiratory disease, nor did any have other recognized disease thought to cause metaplasia or atypical cells in the bronchial mucosa. The authors suggest that some aerosol products either alter the flora of the bronchial tree or contain carcinogenic compounds. Although the authors do not suspect the propellants of being carcinogenic, they do suggest additional testing of them to determine their effects on the quantity and quality of mucus, ciliary activity, and on the susceptibility to infection by microorganisms.

Lebowitz (1976) surveyed 3,485 individuals for frequency and type of aerosol product usage and for respiratory symptoms (such as persistent cough, phlegm, chronic bronchitis, emphysema, etc.). After correcting for age, smoking habits, etc., Lebowitz found that the data suggest a tendency for more symptoms to follow increased aerosol usage, most consistently among non-smokers.

While these studies themselves do not supply much useful information for assessing the hazards associated with exposure to the fluorocarbons from aerosol product usage, they do indicate that further investigation into this area would be prudent.

There has been considerable attention given to the toxic effects of the fluorocarbon anesthetic halothane toward both the patients receiving it and the operating-room personnel. Within a few years following its introduction as a clinical anesthetic (1956 in Great Britain, 1958 in the United States), a substantial number of reports began to appear indicating an association between halothane and post-operative liver necrosis in the patients. Many studies have been made on the incidence of "halothane hepatitis" and the majority of them agree that halothane is hepatotoxic, but that the incidence is quite low in clinical practice.

The National Halothane Study (1969) reported that the incidence of death from massive hepatic necrosis following halothane anesthesia was 1 in 9804 and, excluding those cases which could be attributed to causes other than halothane exposure, the incidence was 1 in 35,250. Noting that mortality is too gross a criterion to assess the toxicity of a substance, Carney and Van Dyke (1972) reviewed data from five other halothane studies and found that the incidence of post-halothane hepatitis (fatal and non-fatal) was 1 in 2725. Mortality rates from these and three additional studies averaged 1 in 11,214, quite comparable to the mortality rate reported by the National Halothane Study. The data reviewed by Carney and Van Dyke do not enable exclusion of factors other than halothane as the causative agent, but assuming that other factors were involved at the same incidence observed in the National Halothane Study, they calculated that the incidence of halothane hepatitis would amount to 1 in 9090, and that the incidence of attendant mortality would be 1 in 40,370.

Carney and Van Dyke (1972) also examined the incidence of fatal and non-fatal liver injury in patients receiving non-halogenated anesthetics. The data showed that the mean hepatitis rate in these patients was 1 in 5,099, with fatalities due to liver injury occurring in 1 of 12,538. The mortality rate was about the same for halothane and non-halogenated anesthetics, while the rate of non-fatal hepatitis with non-halogenated anesthetics was about one half that of halothane (i.e. 1 in 2525). It is, therefore, possible that half of the cases of halothane hepatitis which could not be attributed to factors other than halothane may, in fact, have been due to other indeterminable factors. However, Carney and Van Dyke (1972) did not comment as to whether or not the use of non-halogenated anesthetics in the cases examined was based on prior determination of existing liver impairment or surgical procedures where there is an increased risk of liver injury. Were this the case, the usefulness of these data for comparison to the halothane data would be questionable.

Also questionable is the adjustment of the liver toxicity incidence, as in the National Halothane Study, to exclude all cases where the effect could be attributed to factors other than halothane since this could, in some cases, underestimate the importance of halothane as a contributing factor in the liver toxicity observed.

Although the incidence of post-halothane hepatitis is low and many cases have been studied, there is as yet no clear correlation with other factors which may influence or predispose individuals to its development. One possible correlation considered by clinical studies which is supported by the recent studies of halothane metabolism is inadequate oxygen supply to the liver due to some physiologic reason or the nature of the surgical procedure. Such conditions would, based on the metabolism studies, favor the formation of reactive metabolites which bind to cell constituents. The formation of bound metabolites has been associated with liver toxicity from other compounds, such as carbon tetrachloride, and may well be the cause of halothane liver toxicity also. Another correlation, which would also indicate that bound metabolites are involved, is the observation that the risk of halothane hepatitis in surgical patients is increased with repeated exposures.

In addition to the liver effects of halothane, headache, mood changes, and alterations in intellectual function have been reported to follow halothane anesthesia (Tyrell and Feldman, 1968; Johnstone et al., 1975). These effects may result from the bromide released in the metabolism of halothane. Bromism, or chronic bromide intoxication, is a recognized syndrome characterized by headache, lethargy, dizziness, mental confusion, and other similar signs. Johnstone et al. (1975)

found blood levels of bromide following halothane anesthesia approaching those associated with its psychoactive effects persisting for a week or so after anesthesia.

The manifestation of toxicological effects among anesthetists and other operating room personnel has also received much attention. Ambient concentrations of halothane in operating rooms have been reported to be 10 ppm (Linde and Bruce, 1969), 4.9-8.7 ppm (Whitcher et al., 1971), and 14-59 ppm (Gotell and Sundell, 1972). Halothane is usually used with nitrous oxide, and there is, therefore, exposure to this gas as well as to halothane in the operating room. In the study noted above, where 10 ppm halothane was measured, 130 ppm nitrous oxide was also found. Other anesthetics, such as methoxyflurane, are also used. Further, there are many non-anesthetic volatile materials to which operating room personnel may be exposed (Jenkins, 1973). Linde and Bruce (1969) also note that there may be significant exposure to radiation among anesthetists. Although exposure to a multiplicity of materials makes it difficult to correlate observed effects among operating room personnel with any specific material, halothane appears to be a common denominator.

The hazards which have been associated with trace anesthetics in operating rooms are reported to be (a) increased risk of spontaneous abortion among exposed pregnant women, (b) increased incidence of congenital abnormalities in children of women who work in operating rooms, (c) increased susceptibility to cancer for female, but not male, anesthetists, and (d) increased risk of liver disease equally applicable to males and females. These findings are from a nationwide survey of operating room personnel (Anonymous, 1974).

Cohen et al. (1971) reported a 37.8% abortion rate among anesthetists compared with a 10.3% abortion rate for a control group comprised of physicians in non-anesthesia specialties, and a 29.7% abortion rate among operating room nurses, compared with 8.8% for a control group of general duty nurses. With regard to birth defects, a study by Corbett (1974) showed that 71 of 434 children (16.4%) born to nurse anesthetists who continued to work during pregnancy had congenital abnormalities, whereas 15 of 261 children (5.7%) born to nurse anesthetists not working during pregnancy had anomalies. Significant increases were observed in the incidence of hemangiomas, total skin anomalies, inguinal hernias, and musculoskeletal anomalies among the children of mothers who continued working. Slight, but not statistically significant, increases were also observed in the incidence of cardiovascular, gastrointestinal, and central nervous system anomalies.

Bruce _et_ _al_. (1974) reported that in a controlled study of humans inhaling 15 ppm halothane with 500 ppm nitrous oxide, significant decrements were observed in the performance of tasks in which attention was divided between auditory and visual signals, a visual tachistoscopic test and memory tests involving digit span and recall of word pairs, when compared to controls breathing only air. Subjects receiving 500 ppm nitrous oxide showed decrements only on the digit span test, and the authors concluded that the other effects were likely due to halothane.

In animal studies described in subsequent sections, chronic exposure to trace amounts of halothane (10 ppm) is shown to result in changes in liver, kidney, and the central nervous system of adult and developing animals. These studies support the association of hazards to operating room personnel with halothane exposure.

X. EXPERIMENTAL TOXICITY STUDIES

A. Inhalation

1. Acute Exposure

The commercially important fluorocarbons have been tested to some extent for acute inhalation toxicity. Results are presented in Table B-I (Appendix B). In that many of these tests were conducted to determine the potential hazard from occupational exposure, or to determine anesthetic potency, the response of the animals is often measured in terms of effects such as tremors, convulsion, and loss of righting reflex as well as lethality. In Table B-I, the approximate lethal concentration (ALC) is the minimum concentration causing death in any of the animals over the exposure period, which is usually less than the concentration causing death in half of the test animals (LC_{50}). The anesthetic concentration is that at which certain basic reflexes are lost. The concentration causing tremors usually represents the minimum concentration causing any marked response. Nonlethal concentrations represent levels not causing death in the exposure period and, in cases where it is less than the concentration causing tremors, it is an approximation of the "no marked effect" level.

The fluorocarbons showing the greatest acute inhalation toxicity are F-11 and F-113, where exposures of 5-25% are fatal. By contrast, the other fluorocarbons shown in Table B-I do not elicit lethal responses at concentrations from 40% to 80% or more. Since concentrations of fluorocarbons in ambient air are in the parts per billion and less range, and may reach only a few hundred parts per million (less than 0.1%) in a small room where a fluorocarbon-propelled aerosol is used, there is little reason to be concerned with acute inhalation toxicity of the fluorocarbons in terms of lethality under normal use conditions. However, acute inhalation of the fluorocarbons has been shown to affect certain cardiovascular and pulmonary parameters, which are discussed in Section XI of this report.

2. Subacute Exposure

The distinction between subacute and chronic exposure to a substance is usually an arbitrary one, involving consideration of such parameters as duration, frequency, and number of exposures. For the purposes of this paper, chronic exposures are taken as those lasting for at least 6 hours per day and continued for at least 30 days, which is somewhat similar to occupational exposures. Exposures not fitting these criteria are here classified as subacute.

Subacute inhalation toxicity data are presented in Table B-II. No significant signs of toxicity were noted in animals exposed to F-11 with the possible exception of rats exposed to 1.2% F-11 for 4 hours per day for 10 days, where, among other pathological changes, emphysema and lung edema were observed. However, no changes were noted in dogs exposed to 1.25% or in cats exposed to 2.5% F-11 for 3.5 hours per day for 20 days (Clayton, 1966).

Subacute exposure to F-113 showed some possible liver toxicity rats to at 6% and 4% administered one hour per day for five days.

F-114 was fatal to 4 of 4 dogs exposed 8 hours per day to 20% for 3 or 4 days. All animals died during exposure. However, dogs exposed to 14.16% F-114 for 8 hours per day developed a tolerance to the exposure after three days, and showed no significant toxicological effects after 21 days.

Ross and Cardell (1972) have demonstrated that rats inhaling 0.25% halothane in air 7 hours per day for 7 days develop hepatic lesions. Hughes and Long (1972) observed hepatic necrosis in 7 of 50 guinea pigs anaesthetized 1-5 times with 1% halothane in oxygen.

3. Chronic Exposure

In assessing the environmental hazards posed by the fluorocarbons from a health effects standpoint, the most valuable type of studies is that dealing with long-term inhalation exposure to the materials at levels below which symptoms of acute toxicity occur, preferably at levels approaching those to which many persons are continually (or consistently) exposed (probably in the parts per billion range by volume according to the data of Hester et al. (1974)). Unfortunately, studies at these low concentrations have not been carried out to date and except for one 10-month study with F-22, "long-term" studies have been on the order of 90 days or less. Data are presented in Table B-III.

The earliest investigation into chronic inhalation toxicity of a fluorocarbon material was reported by Sayers et al. (1930) where dogs, monkeys, and guinea pigs were exposed to 20% F-12 for 7-8 hours a day for 5 days, and 4 hours for 1 day each week over a 12-week period. The animals were observed for lethality, changes in behavior, weight gain, red and white blood-cell count (including differential), and autopsy findings. Tremors were observed in the dogs and, to a lesser extent, in the monkeys during exposure periods. After two weeks of exposure, the animals appeared to develop a tolerance to F-12 as the amount and degree of tremors declined. These animals showed a depression in weight gain compared to controls during the early part of the study, which was less significant after the tolerance to development of tremors occurred. This was probably associated with depressed appetite and/or increased energy expenditure during the period when tremors were prevalent. Guinea pigs did not develop tremors, although some irritation was observed. None of the exposed or control monkeys and dogs died during the study. Ten of twenty-six exposed guinea pigs and six of twenty-six control guinea pigs died during the study. The cause of death among all of these animals was congestion and edema of the lungs and pneumonia. All but three of these deaths (1 control, 2 exposed) occured among eleven animals from each group used to obtain blood samples throughout the test. The deaths of these animals were attributed to either handling technique during blood extraction and/or increased exposure to other factors which influence respiratory illness in guinea pigs. It was noted that these studies were performed in the winter when respiratory illness is prevalent among guinea pigs.

Red blood cells and hemoglobin showed a slight increase during the first two or three weeks of exposure, but were normal and similar to controls thereafter. White cell counts were the same for exposed and control animals, although differential white cell examinations showed a slight increase in polymorphonuclear neutrophils and a slight decrease in lymphocytes of the exposed animals. Autopsies revealed no pathological changes in the exposed animals (other than that mentioned above for the guinea pigs). It was also noted in this study that the frequency of pregnancy and bearing of normal young were similar for exposed and control guinea pigs.

Prendergast et al. (1967) also studied chronic inhalation toxicity of F-12 using rats, guinea pigs, dogs, monkeys, and rabbits exposed to 0.081% concentration continuously for 90 days and, in another study, to 0.084% F-12 for 8 hours per day, 5 days a week for six weeks. In the continuous exposure study, 2 of 15 rats and 1 of 15 guinea pigs died, but no other visible signs were observed. There was a high incidence of varying degrees of lung congestion in rabbits, monkeys, rats, and guinea pigs. Non-specific inflammatory changes were observed in the lungs of all species, but were also noted for controls. The incidence of this inflammatory change was not mentioned for experimental or control animals. Slight to extensive fatty infiltration of the hepatic cells was observed in all exposed guinea pig liver sections examined and several sections exhibited focal or submassive liver necrosis. These liver changes in guinea pigs were considered to have been induced by the exposure. In the repeated exposure study, lung congestion and non-specific inflammatory changes were observed. Several guinea pigs were found to have exposure-related focal necrosis or fatty infiltration of the liver and one monkey had heavy deposits of pigment in the liver, spleen, and kidney.

Jenkins et al. (1970) studied the chronic inhalation toxicity of F-11 in rats, guinea pigs, monkeys, and dogs at 0.1% concentration for 90 days or with 8-hour exposures of 1.025% for 5 days per week for six weeks. One monkey in the continuous 90 day exposure study died, showing hemmorrhagic lesions on the surface of the lung. The authors state that necropsy failed to reveal any evidence that death was directly attributable to F-11 exposure. They do not, however, present any arguments that the death was attributable to other factors. In monkeys surviving continuous exposure, a large amount of inflammatory infiltration was noted, occasionally associated with microfilarial parasite infestation. Blood smears showed such parasites in approximately half of the experimental and control animals. There were no remarkable differences in response between the continuous and repeated exposure groups. Non-specific inflammation of the lungs was evident in all experimental species, except in dogs given repeated exposure. Such changes were not described for control animals. Mild discoloration was noted in the livers of one-fourth of the rats and guinea pigs in both exposure groups. A single 2 x 4 mm liver lesion was noted in one of the male rats from the continuous exposure groups. Of eight rats examined after repeated exposures, one evidenced focal myocytolysis and two showed focal non-specific myocarditis. Marked increases in serum urea nitrogen were noted in dogs exposed continuously (33 mg/100 ml) and repeatedly (36 mg/100 ml), compared to controls (16.8 mg/100 ml). No change in serum urea nitrogen was observed in any other animals in either exposure group.

Clayton (1966) referenced a study by Karpov (1963) exposing rabbits, rats, and mice to 1.42% F-22 for 6 hrs/day for 10 months. Mice showed lower endurance in a swimming test and an increase in the number of trials needed to establish a conditioned reflex. Rats showed a decrease in oxygen consumption and an increase in subthreshold stimuli needed to induce a response. Rabbits showed decreases in red blood-cell count, hemoglobin, lymphocytes, reticulocytes, blood cholinesterase, and serum albumin and increases in neutrophiles, eosinophiles, and globulin. Pathological examination revealed degenerative changes in heart, liver, kidney, and nervous system as well as changes in lungs leading to emphysema and exudate alveolar septal thickening. None of the aforementioned changes were observed in rabbits, rats, or mice exposed to 0.198% F-22 for the same duration.

Three of twenty-one rats exposed to F-113 for 7 hours per day for 31 days showed slightly pale livers, but no other remarkable observations were made for F-113, or for chronic inhalation studies of F-115 and F-13B1 (Clayton, 1966).

Chronic inhalation studies with halothane have shown effects in the liver, kidney, and nervous system detectable at the ultrastructural level with electron microscopy. Adult rats exposed to 10 ppm or 500 ppm halothane for 8 hours per day, 5 days per week for 8 and 4 weeks, respectively, developed pathological changes in the hepatocytes including crenation of the nucleus, glycogen depletion, dense and c-shaped transformation of the mitochondria, disorientation or condensation of the rough endoplasmic reticulum, and coagulative necrosis of the hepatocytes (Chang et al., 1974a). Chang et al. (1975a) found that rats exposed to 10 ppm halothane for 8 hours per day, 5 days per week for 8 weeks developed chronic degenerative changes in the kidney. Pathological changes in the kidney were even more extensive and pronounced in rats exposed to 500 ppm, 8 hours per day, 5 days per week for 4 weeks. Chang et al. (1974b) report that exposures of halothane to rats at 10 ppm for 8 hours per day, 5 days per week for 8 weeks caused ultrastructural changes in the nervous system such as collapse of the neuronal rough endoplasmic reticulum, dilation of the Golgi complex, and focal cytoplasmic vacuolation within cortical neurons. Again, more extensive damage was observed in rats receiving 500 ppm for 8 hours per day, 5 days per week for 4 weeks. The levels of halothane used in these studies were chosen as representative of levels found in operating rooms and support the contention that halothane is a causative and/or contributory factor in certain effects observed in operating room personnel.

The type of studies which have been performed to date do not form an adequate data base for assessing the health hazards associated with continual environmental exposure to the commercially important fluorocarbons such as F-11, F-12, etc. The observed effects with halothane and the findings such as inflammatory infiltration of the lung and liver changes noted in some of studies with the other fluorocarbons do indicate that long-term inhalation of these materials at levels below those associated with more acute types of responses (tremors, cardiac effects, etc.) may not be inconsequential. Chronic inhalation studies with much longer exposure periods to the commercial fluorocarbons than those performed to date and at low levels, that is, the parts per million range, are needed. These studies should include electron microscopic examination of tissues for ultrastructural changes at the cellular level.

B. Dermal Exposure

Clayton (1966) reported that the approximate lethal dose of F-113 applied to the skin of rabbits was greater than 11 g/kg, with local irritation of the skin at the application site and alterations in the dermis and adjacent connective tissues. No systemic changes were observed. F-113 applied to rabbit skin at a dose of 5 g/kg daily for five days results in fluctuations in weight and damage to the skin. Slight liver changes were observed microscopically but no other systemic changes were observed. Fluorocarbon-113 has been applied to the shaved back of rabbits five times a week for twenty weeks with no visible adverse affects (Desoille et al., 1968).

Fluorocarbons-11, -12, -113, or -114 at 40% in sesame oil sprayed daily for 12 days on rabbits (shaved skin) elicited no effect (Scholz, 1962). Quevauviller et al. (1964) and Quevauviller (1965) have applied F-11, F-12, F-114, and mixtures of F-11 and F-12, and F-11 and F-22 to the skin, tongue, soft palate, and auditory canal of rats 1-2 times per day for 5 days per week for 5-6 weeks. Each compound was sprayed on the surface for five or ten seconds from a distance of 10-20 cm. Skin irritation with edema and a slight inflammatory reaction was observed, most markedly with the F-11/F-22 mixture. Older rats were more severely affected than younger rats. The auditory canal of one rat treated with F-114 showed desquamation of the epithelium and inflammation. No significant changes were observed in the other areas of application with these materials. The healing rate of burns was retarded by application of all the above fluorocarbons.

The rapid evaporation of the fluorocarbons from the skin surface may result in chilling or freezing of the tissue and is, perhaps, the principal hazard associated with acute dermal exposure. Since edema is often an early symptom of frostbite, it is possible that part or all of the skin reactions noted above were due to this evaporative effect. Evaporative effects are not as significant a factor in dermal exposure to the less volatile fluorocarbons, notably F-113. As indicated previously, F-113 is absorbed through the skin, being detectable in the exhaled air of dermally exposed individuals.

C. Oral Exposure

Because of their uses and physical properties, oral exposure to the fluorocarbons is unlikely and little information is available. F-11 was not fatal to rats receiving 7.38 g/kg via intubation, nor were there any histological changes in the liver (Slater, 1965). Clayton (1966) reported approximate lethal dose values in rats of 1 g/kg for F-11 and 2.25 g/kg for F-114 disolved in peanut oil. Both Clayton (1966) and Michaelson and Huntsman (1964) report the approximate lethal oral dose of F-113 in rats to be 45 g/kg.

No adverse effects were observed in rats receiving oral doses of 2 g/kg/day of F-114 for 23-33 days (Quevauviller, 1965). No evidence of toxicity was found in rats receiving oral doses of 140-170 mg/kg/day of F-115 for 10 days (5 days per week for 2 weeks) (Clayton, 1966).

Fluorocarbon-12 is the only major fluorocarbon compound for which chronic oral toxicity data have been reported. Waritz (1971) summarizes the results of a 90-day feeding study with rats at doses of 35 and 350 mg/kg/day and dogs at doses of 10 and 100 mg/kg/day. No deviations are noted from either control groups except that experimental rats had elevated but not abnormal levels of urinary fluoride and plasma alkaline phosphatase.

Sherman (1974) conducted a two-year feeding study of F-12 in rats and dogs. The approximate dose levels for rats were 15 mg/kg/day and 150 mg/kg/day, administered as a corn oil solution via gastric intubation. There was a slight decrease in body weight gain in the high dose groups of rats, but there were no clinical signs of toxicity and liver function, urine, hematological, and histopathological analyses were within normal limits as established by controls. In the dog studies, the F-12 was administered by immersion of Gainesburgers^R into F-12, and the average doses were approximately 8 mg/kg and 80 mg/kg for the low and high dietary levels, respectively. There were no signs of toxicity or changes in the analyses of liver function, urine, hematological or histopathological parameters. There was an apparent retention of some F-12 (up to 1 ppm) in the fat and bone marrow.

D. Carcinogenicity

Epstein et al. (1967) found that F-11, F-113 and F-112 ($C_2F_2Cl_4$) at doses of 0.1 ml of 10% (v/v) solution in redistilled tricaprylin injected subcutaneously in the neck of neonatal mice are not carcinogenic. However, when injected in conjunction with a 5% (v/v) solution of piperonyl butoxide, F-113 and F-112 were found to induce hepatomas in male mice. (F-11 was not tested with piperonyl butoxide.) Piperonyl butoxide, which alone was not hepatotoxic or hepatocarcinogenic, is a potent inhibitor of microsomal enzyme function (detoxification) in insects and is thus a useful synergist with insecticides. Piperonyl butoxide is also a potent inhibitor of microsomal enzyme systems in mice, but is much less potent in rats and humans (Conney et al., 1972). While it is impossible to interpret the significance of this one study in terms of exposure to the fluorocarbons, it is indicative of a possible synergistic effect between these compounds and microsomal enzyme system inhibitors and remains an avenue of future study.

At this time, F-11 is being tested for carcinogenicity by gastric intubation at Hazelton Laboratories. Fluorocarbon-12, while not on test currently, has been approved for testing via the inhalation route (Kraybill, 1975).

E. Reproductive Effects, Mutagenicity, and Teratogenicity

Bruce (1973) found no reproductive effects in rats exposed to 16 ppm halothane in air, 7 hours per day, 5 days per week for 6 weeks prior to mating. Wittmann et al. (1974) reported that female rats exposed to 0.8% halothane in nitrous oxide-oxygen for 12 hours per day on gestation day 6 and 10 had an abortion rate of 44%, compared to 13% among controls receiving nitrous oxide-oxygen. Kennedy et al. (1976) found no adverse effects on fertility or general reproductive performance in rats exposed to anesthetic concentrations of halothane (approximately 1.4%) prior to mating. Kennedy et al. (1976) also found no reproductive or teratogenic effects of halothane in rats or rabbits exposed to anesthetic concentrations of halothane during gestation.

In three similar studies in which pregnant rats were exposed to 10 ppm halothane for 8 hours per day, 5 days per week throughout pregnancy, no effects were reported in the number of offspring nor were there any reported grossly observable teratologic effects. However, pathological changes were observed with electron microscopy in the offspring of the halothane treated mothers as follows: degenerative changes in the liver (Chang et al., 1974c); kidney lesions confined to the proximal convoluted tubules (Chang et al., 1975b); and significant pathological changes in the nervous system, such as weakening of the nuclear envelope of many neurons, dilation and vacuolation of the Golgi complex, and occasional cell death in the neonatal cortex (Chang et al., 1976). Enduring learning deficits associated with ultrastructural evidence of nervous system damage in rats exposed to halothane from conception to day 60 of age are discussed in the following section, Behavioral Effects.

Using a dominant lethal test, Sherman (1974) found that F-12 displayed no mutagenic activity in rats during a two-year feeding study at doses of 15 or 150 mg/kg/day. Administration of F-12 to parent male and female rats had no effect on fertility or the outcome of pregnancy, as measured by the number of corpora lutea, implantation sites, resorption sites, and number of live fetuses per litter.

F. Behavioral Effects

Quimby et al. (1974) reported that rats exposed to halothane from conception through day 60 of age (dam or neonate exposed to approximately

10 ppm halothane in air, 8 hours per day, 5 days per week) and rats exposed to halothane from conception to 130-150 days of age exhibited deficits in learning shock-motivated light-dark discrimination and food-motivated maze patterns, when compared to either controls with no halothane exposure or a group of rats that were exposed to halothane from day 60 of age through day 130-150. These learning deficits were correlated with electron microscopic evidence of neuronal degeneration, and permanent failure of formation of the synaptic web and postsynaptic membrane density in 30% of the postsynaptic membranes. Only slight neuronal damage was evident in the rats exposed from day 60 on. The data indicate that early exposure to halothane, either in utero or as a neonate, causes apparently permanent learning deficits since, in the first group of rats described above, halothane exposure was ended at 60 days of age, yet the deficits were apparent 75-90 days after termination of exposure when the behavioral testing was conducted.

Karpov (1963) reported an increase in the number of subthreshold impulses needed to produce a reflex in rats and an increase in the number of trials needed to establish a conditioned reflex in mice with exposure to 1.42% F-22 6 hours/day for 10 months. These effects were not observed with an exposure level of 0.198%. Carter et al. observed significant performance decrements in trained monkeys exposed to 20-25% F-13B1 without indications of analgesia or CNS depression.

The anaesthetic and intoxicant properties of the fluorocarbons were mentioned earlier (Section X). The effects of fluorocarbons on psychomotor test scores in humans and the feelings of drowsiness and loss of orientation by human test subjects were also mentioned earlier (Section IX.).

G. Phytotoxicity

Unpublished experiments (Taylor, 1974) indicate that F-11 and F-12 at concentrations of 0.5-1, 10, or 15 ppm for two weeks were not toxic to plants.

H. Toxicity to Microorganisms

The comparative toxicity of F-12 and F-142b ($CClF_2$-CH_3) have been determined in liquid and vapor states for a variety of microorganisms (Prior et al., 1970). Of the eighteen species tested, seven species grew as well in contact with gaseous F-12 or F-142b as in their absence (different groups for each fluorocarbon). In no instances were substantial growth reductions noted. However, in the liquid state both F-12 and F-142b substantially reduced cell viability in all cultures tested. Because agitation is required to induce the toxic effects, Prior et al. (1970) conclude that there is probably some interaction between the compounds and the lipids in the microorganisms.

XI. CARDIOVASCULAR EFFECTS

In Section IX, Human Toxicity, it was mentioned that the fluorocarbons were responsible for several deaths associated with the intentional inhalation of fluorocarbon propelled materials by individuals attempting to achieve an intoxicated state. Bass (1970) concluded from a study involving more than 50 such deaths (as well as more than 50 additional non-fluorocarbon related fatalities involving the inhalation of volatile materials) that the cause of death was most probably due to cardiac arrhythmia, possibly aggravated by elevated levels of blood catecholamines due to stress, and/or moderate increases in the blood level of carbon dioxide.

A. Cardiac Arrhythmia

Subsequent to the report by Bass (1970), the cardiac arrhythmogenic potential of fluorocarbons has received considerable investigation. Cardiac arrhythmia, as the name implies, is the occurrence of an abnormal excitatory pattern within the heart. It may result from a disturbance of the generation of the heart's impulse in the sinoatrial node, a disturbance of the spread of this impulse through the conducting system of the heart, or the generation of an impulse at any site in the heart other than the sinoatrial node. Arrhythmias result in less efficient cardiac function and may result in complete cardiac arrest.

The first report of cardiac arrhythmia in test animals following inhalation of fluorocarbons was that of Taylor and Harris (1970a), who described the effect in mice exposed to F-11, F-12, and F-114. This study was designed to show that the fluorocarbons tested were sensitizing the heart to the arrhythmogenic effect of asphyxia. Asphyxia results in a lowering of the oxygen tension which increases the heart rate (tachycardia). However, the heart, being unable to acquire an oxygen debt, will slow (bradychardia) and eventually fail. The sensitization effect implies that a degree of asphyxia that will not result in arrhythmia in normal animals will induce arrythmia in sensitized animals. A controversy ensued over the Taylor and Harris experiment concerning whether or not the degrees of asphyxia applied to the experimental and control groups were equivalent. Other workers, including Azar et al. (1971), Egle et al. (1972) and McClure (1972) report that the fluorocarbons do not significantly influence the cardiac response of mice to asphyxia. Flowers and Horan (1972) exposed dogs to fluorocarbon-propelled aerosol products (F-11 and F-12; amount not stated) and carefully controlled the level of oxygenation to determine what effect asphyxia played in the arrhythmias. They found that lethal arrhythmias were produced even in the absence of asphyxia, indicating that asphyxia may have played only a contributory role in the fluorocarbon-propelled aerosol deaths, but was not necessary for production of the fatal arrhythmias. The ability of various fluorocarbons to induce arrhythmias in different species is summarized in Table C-I (Appendix C).

In addition to suggesting the influence of asphyxia in the fluorocarbon propelled aerosol inhalation deaths, Bass (1970) also postulated that the induction of arrhythmias was enhanced by elevated blood levels of catecholamines. It has long been known that the inhalation of certain volatile hydrocarbons can sensitize the heart to epinephrine-induced cardiac arrhythmia. Epinephrine, a catecholamine often referred to as adrenaline, is a potent adrenal cortical hormone which has a variety of cardiovascular effects, chief among which are vasoconstriction (resulting in increased blood pressure) and increases in both the heart rate and cardiac output. In man, the blood plasma concentration is approximately 0.06 μg/l and, under conditions of stress, the adrenal gland may secrete epinephrine at the rate of 0.004 mg/kg/minute. Excesses are rapidly eliminated from the body. Abnormally high blood levels may elicit adverse effects including cardiac arrhythmia (ventricular). The sensitizing effect, similar to that mentioned before for asphyxia, means that during or immediately following exposure to a sensitizing substance, blood levels of epinephrine which would otherwise have no adverse effects, may result in cardiac arrhythmia and possibly cardiac arrest.

In Table C-II, the effects of fluorocarbons on sensitizing the heart to an injection of epinephrine are summarized. An important parameter here is the amount and rate of epinephrine infusion, chosen in these studies at levels found to be non-hazardous and productive of only transient and moderate cardiac acceleration and which simulate the quantities of epinephrine known to be released endogenously under conditions of fright. The results show basically that inhaled concentrations of fluorocarbons which sensitize the heart to epinephrine-induced arrhythmias are lower than those required to induce arrhythmias themselves. For example, exposure to 5% of F-11 or F-113 by inhalation sensitizes mice to epinephrine; exposure to 10% of these compounds is necessary for induction of arrhythmias in this species without epinephrine. This effect is also seen in monkeys exposed to F-11 or F-12. Certain fluorocarbons which do not induce arrhythmias in mice at exposures of 40% (F-22, F-114, F-115, and F-152a) do sensitize mice to epinephrine induced arrhythmias, although the required fluorocarbon concentrations are still relatively high (20% or more). Also noteworthy is the high sensitivity of dogs to the epinephrine sensitization effect of F-11 and F-113; unfortunately, the amount of fluorocarbon which causes arrhythmias in this species without epinephrine has not been reported.

In order to better assess the relevance of the studies using injected epinephrine to conditions of actual stress, experiments have been designed to measure the arrhythmic effect of fluorocarbons on dogs presumably releasing high levels of endogenous epinephrine. These include the studies by Reinhardt et al. (1971) where dogs were "frightened" by loud amplified noises and the study of Mullin et al (1972) where dogs were run on a treadmill under conditions previously reported to increase blood epinephrine levels five-fold. In general, the results of these studies indicate that somewhat higher concentrations of fluorocarbons are necessary for the production of arrhythmias than in the exogenous epinephrine experiments.

For example, in the noise experiments of Reinhardt et al. (1971), dogs were exposed to 80% fluorocarbon/20% oxygen for 30 seconds which results in arrhythmias with F-11, F-12, and F-114. However, because each of these compounds is capable of inducing arrhythmias in other species at lower concentrations without epinephrine sensitization, it is difficult to assess the significance of this experiment. In the treadmill experiments concentrations of 0.5%, 0.75%, and 1.0% F-11 produced no response. One of six dogs exposed to 10% F-12 developed arrhythmias, but no effects were observed at 5% or 7.5% levels. With F-114, one of seven dogs developed arrhythmias when exposed to a concentration of 5%, but no response was observed at the 2.5% level.

The above studies show that there is little doubt that the deaths of persons intentionally inhaling fluorocarbon-propelled aerosol products are attributable to the cardiac toxicity of the fluorocarbon propellants and that the original postulates of Bass (1970) were accurate.

B. Respiratory and Other Cardiovascular Effects

Although the major focus of research into the toxicological aspects of the fluorocarbons in recent years has been on the cardiac arrhythmia potential of these materials, Aviado and his coworkers at the University of Pennsylvania School of Medicine have also investigated the effects of the fluorocarbons on other cardiovascular and respiratory parameters. The parameters which have been measured and reported are heart rate increase (tachycardia), depression in myocardial contractility (the force of contraction of the heart measured by a strain gauge), decrease in atrial and pulmonary arterial blood pressures, depression of the respiratory rate, increase in pulmonary constriction, and decrease in pulmonary compliance. The results of these studies are summarized in Table C-III. The purpose of these studies was to a large extent to determine what role the fluorocarbons may have played in the deaths of asthmatics using fluorocarbon-propelled bronchodilators. Although bronchoconstriction and respiratory depression do occur with acute inhalation of these compounds, they occur at concentrations which are similar to the arrhythmia-causing concentrations of the more potent inducers of arrhythmia (F-11 and F-113) and at concentrations of 10% to 20% among those fluorocarbons that either do not elicit arrhythmias or do so only at high concentrations. These data indicate that the primary hazard associated with F-11 inhalation, whether by misuse of aerosol products or overuse of F-11 propelled bronchodilators remains the production of cardiac arrhythmias. However, the data also indicate that, at least for abusive inhalation, the non-arrhythmogenic fluorocarbons or those with low arrhythmogenic activity are not without other potentially adverse toxicological properties.

C. Classification of Fluorocarbons Based on Cardiac and Pulmonary Effects

Based on animal studies (mice, rats, dogs and monkeys) of the cardiac arrhythmia effects discussed above, as well as the effects of fluorocarbons on other cardiac and respiratory parameters, Aviado (1975b) has proposed a scheme for classifying the fluorocarbons. This classification also includes four non-fluorocarbon aerosol propellants (trichloroethane, methylene chloride, isobutane, propane, and vinyl chloride) and a four-carbon cyclic fluorocarbon (octafluorocyclobutane) which are outside the scope of this report, but are included in this discussion for the sake of completeness.

There are four categories into which the aerosol propellants fall; descriptions of these categories and the compounds placed in each are as follows:

1. Low pressure propellants of high toxicity (F-11, F-21, F-113, trichloroethane and methylene chloride). The characteristics of this class are that they exert their toxicity at concentrations of 0.5-5% in the monkey and dog, and from 1-10% in the rat and mouse. They induce cardiac arrhythmias, sensitize the heart to epinephrine-induced arrhythmias, cause tachycardia (increased heart rate), myocardial depression (force of mycardial contraction measured by strain gauge), and hypotension (as measured by aortic, left atrial, and pulmonary

arterial blood pressures). The predominant effects of this class are on cardiovascular parameters rather than on respiratory parameters.

2. Low pressure propellants of intermediate toxicity (F-114, F-142b, isobutane, and octafluorocyclobutane). Compounds in this class differ from those above in the following respects. Concentrations of these compounds that sensitize the dog to epinephrine range from 5-25%, compared to 0.5% or less for compounds in the high toxicity class. These compounds do not induce arrhythmias in the mouse, whereas the high toxicity compounds do so at concentrations of 10-40%. Concentrations of 10-20% influence circulation in the anesthetized dog and monkey, compared to concentrations of 0.5-2.5% of the high toxicity group which cause these effects. Lastly, these compounds cause bronchoconstriction in the dog, an effect not observed with the high toxicity compounds. On all accounts except the last, these compounds are less toxic than those in the first group.

3. High pressure propellants of intermediate toxicity (F-12, F-22, propane, and vinyl chloride). Although the concentrations of these compounds that sensitize the dog to epinephrine and the concentrations that influence circulation in the monkey and dog are similar for these compounds and those in the above category, they differ in their effects on the respiratory parameters. The compounds in this class cause early respiratory depression and bronchoconstriction which predominate over their cardiovascular effects. In both of the preceding groups, cardiovascular effects predominate.

4. High pressure propellants of low toxicity (F-115 and F-152b). These compounds differ from those above in that they do not cause bronchoconstriction or early respiratory depression. The extent of the effects of these compounds on circulation is also less than those in the group above.

Aviado (1975a) has further concluded on the basis of these results that F-11 is the most toxic of the aerosol propellants, and the most serious toxic effects are the induction of cardiac arrhythmia and the sensitization of the heart to the arrhythmogenic effects of epinephrine.

D. Increased Sensitivity In Diseased Animals

There have been a few studies published which consider the predisposition of test animals with cardiac or pulmonary disease to the toxic effects of fluorocarbons. Taylor and Drew (1975) compared the effects of F-11 in normal random-bred hamsters to those observed in the BIO 82.62 strain of Syrian hamster which possess cardiomyopathy as an inherited trait. These particular hamsters develop cardiac hypertrophy and at the age of 240 days they experience frank congestive heart failure. F-11 concentrations of 2% or 7.5% were not lethal to normal hamsters at age 150 or 240 days, nor to cardiomyopathic hamsters at age 150 days. In myopathic hamsters of 240-day age, 4 of 5 died within 48 minutes of exposure to 2% F-11, the survivor dying 2 days later, and 4 of 4 died within 30 minutes when exposed to 7.5% F-11. Myopathic hamsters of 240 days age exposed to room air or to a 7.5% nitrogen placebo survived an average of 8.1 and 9.5 days post-exposure, respectively. All of the preceding were 4-hour exposures.

Cardiomyopathic hamsters were also more sensitive to the arrhythmogenic effects of F-11. Using five-minute exposures to 2.5% or 5% F-11, no arrhythmias were observed in 120 or 180 day old normal hamsters. With the cardiomyopathic hamsters, arrhythmias were observed in 4 of 4 120 day old animals exposed to 2.5% F-11 and also in 4 of 4 120 day old animals exposed to 5% F-11. In the 180 day old myopathic hamsters, arrhythmias were observed in 1 of 4 exposed to 2.5% F-11 and 5 of 6 exposed to the 5% level. No arrhythmias were observed in normal or myopathic hamsters exposed to 7.5% nitrogen placebo, nor in normal 180 day old hamsters exposed to 7.5% F-11. Exposure of normal 180 day old hamsters to 10% F-11 did result in arrhythmias in 4 of 4 animals. The authors caution that since no known correlation exists between the cardiomyopathic hamster and human heart disease, direct conclusions drawn from these data to increased risk in humans with heart disease is inappropriate. However, the authors state that these data do indicate the possibility of increased toxicity of the fluorocarbons among persons with impaired cardiac function.

Trochimowicz et al. (1976) studied the effect of myocardial infarction in beagles on cardiac sensitization with F-11 or F-13B1 to epinephrine-induced arrhythmias. There was no greater potential for cardiac sensitization in animals having recovered from myocardial infarction (12-13 weeks post-infarction) than normal animals. Tests earlier than 12 weeks post-infarction were not performed.

Brody et al. (1974) have examined the influence of a bronchopulmonary lesion produced by intratracheal injection of 0.2 mg of papain on the cardiopulmonary toxicity of F-11, F-12 and F-152a (difluoroethane) to mice. Animals with lesions did not show an increase in adverse respiratory effects, but did show an increase in adverse cardiac effects. Notably, F-152a, which did not induce arrhythmias and did not sensitize the heart to epinephrine in control mice at 40% concentration, did induce arrhythmias in mice with bronchopulmonary lesions which were not further provoked by epinephrine adminstration.

Doherty and Aviado (1975) induced cardiac necrosis in rats by four daily intramuscular injections of isoproterenol, which decreased the minimal concentration of F-11 that provoked cardiac arrhythmias, although there was no increased sensitivity to F-12 or F-152a. They did observe increased sensitivity to the cardiovascular effects of F-11, F-12 and F-152a in rats pretreated with hexachlorotetrafluorobutane, which induced thrombosis of the pulmonary arteries.

Watanabe and Aviado (1975) produced pulmonary emphysema in rats and found a decrease in pulmonary compliance (27%) upon exposure to F-11 compared to a decrease of 13% in control rats. Inhalation of 40% F-12 caused electrocardiographic abnormalities (ventricular extrasystoles) in emphysematous rats which were not observed in control rats. Inhalation of 10% F-11 and 40% F-12 resulted in tachycardia and abnormal heightening of the QRS potential in emphysematous rats which did not occur in controls.

XII. REGULATIONS AND STANDARDS

With the exception of FDA regulations permitting the use of F-12 as a direct contact freezing agent for food and F-115 for sprayed or foamed foods, there are no current regulations controlling the fluorocarbon compounds. Hearings were held in December 1974 before the House Subcommittee on Public Health and Environment regarding the potential threat of continued fluorocarbon use to stratospheric ozone. Regulatory alternatives and Federal authority are discussed in a report on the fluorocarbon/ozone issue prepared by the Interagency Task Force on Inadvertent Modification of the Stratosphere (IMOS) (1975). Currently, no one regulatory authority has jurisdiction over all uses of the fluorocarbons thay may result in their release to the environment, although various authorities do apply to certain applications. EPA, under the Federal Insecticide, Fungicide, and Rodenticide Act, has the authority to control fluorocarbon uses in pesticide applications and has recently requested pesticide formulators to seek suitable substitute propellants for existing and proposed new insecticide products dispensed as aerosols. (This was in the form of a notice, PR Notice 75-6, December, 1975, not a regulation.)

Though not specific for products containing fluorocarbons, all pressurized containers must meet ICC regulations for compressed gases to be shipped.

Two standards are commonly employed in classifying exposure limits to the fluorocarbons: Threshold Limit Values (TLVs) and the Underwriters' Laboratories Classification. TLVs are assigned by the American Conference of Governmental Industrial Hygienists. Most of the current values were assigned in 1968, but periodic updates are made if warranted by new information. The values, usually expressed in parts per million, represent the maximum concentration that should be present in the working environment. In cases where toxicological information would indicate high acceptable concentration, these values are based on good manufacturing practice. Concentrations higher than

1000 ppm for any compound being used indicate poor production or handling technique and this concentration is thus the upper limit of acceptability. The definitions by the Underwriters' Laboratories in their classification are given in Table XI (Underwriters' Laboratories, 1971). The Underwriters' Laboratories Classification and TLVs for the various fluorocarbons under consideration in this review are given in Table XII.

TABLE XI.

Underwriters' Laboratories Comparative Toxicity Classification of Refrigerants

Toxicity Group	Concentration Per Cent by Volume	Duration of Exposure to Produce Death or Serious Injury to Test Animals
1	½ to 1	5 minutes
2	½ to 1	½ hour
3	2 to 2½	1 hour
4	2 to 2½	2 hours
5	Intermediate between Groups 4 and 6	
6	20	No injury after 2 hours

TABLE XII.

TLVs and Underwriters' Laboratories Classification for Various Fluorocarbons.

Compound	Code	Threshold Limit Value[1]	Underwriters' Laboratories Classification[2]
$CC\ell_3F$	F-11	1000*	5
$CC\ell_2F_2$	F-12	1000	6
$CC\ell F_3$	F-13	(1000)*	6
CF_4	F-14	(1000)*	6
$CHC\ell_2F$	F-21	1000	4-5
$CHC\ell F_2$	F-22	(1000)	5
$CC\ell_2F-CC\ell_2F$	F-112	500	
$CC\ell_3-CC\ell F_2$	F-112a	500	
$CC\ell F_2-CC\ell_2F$	F-113	1000	4-5
$CC\ell F_2-CC\ell F_2$	F-114	1000	6
$CC\ell F_2-CF_3$	F-115		6
$CC\ell F_2Br$	F-12B1		5^+
CF_3Br	F-13B1	1000	6^+
$CBrF_2-CBrF_2$	F-14B2		5^+

[1] A.C.G.I.H., 1973; * Clayton, 1970

[2] Underwriters' Laboratories, 1971a; + Underwriters' Laboratories, 1971b

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Appendix A: Fluorocarbon Absorption/Elimination Data

Table A-I

Absorption/Elimination Data on Various Fluorocarbons Inhaled from Ambient Air

Fluorocarbon	Species	Concentration in Inhaled Air (%v/v)	Duration of Exposure (minutes)	Peak Blood Level (ug/ml)		Time to Peak Blood Level (minutes)	Blood Levels After Exposure (ug/ml)	Time to Reduced Level (minutes after termination of exposure)	Reference
				Arterial	Venous				
F-11	Rats (n=2)	0.23%	5		11.0[illegible] - 11.70	5	0.17 - 0.52	5	Allen and Hanbury's, Ltd. 1971
	"	0.61%	5		22.[illegible] - 31.00	5	2.00 - 2.70	5	" " "
	Rats (anesthetized)	0.64%	5		11.[illegible] - 16.87	5	5.55 - 6.40		" " "
	Rats (n=2)	0.49%	5				0.09 - 0.13	2 hrs.	" " "
	" "	0.49%	5				0.02 - 0.03	4 hrs	" " "
	" "	0.64%	5				0.12 - 0.32	1 hr.	" " "
	" "	0.64%	5				0.007 - 0.014	8 hrs.	" " "
	" "	0.64%	5				0.006 - 0.006	24 hrs.	" " "
	" "	1.00%	5				0.002 - 0.003	48 hrs.	" " "
F-11	Dogs	0.11%	5		4.81	5	1.16 0.42 0.27 0.13	5 10 15 30	" " "
	" "	0.15%	5		5.[illegible]	5	1.32 0.35 0.03 0.02	5 10 15 30	" " "

Table A-I. (cont.)

Absorption/Elimination Data on Various Fluorocarbons Inhaled from Ambient Air

Fluorocarbon	Species	Concentration in Inhaled Air (%v/v)	Duration of Exposure (minutes)	Peak Blood Levels (ug/ml)		Time to Peak Blood Level (minutes)	Blood Levels After Exposure (ug/ml)	Time to Reduced Level (minutes after termination of exposure)	Reference
				Arterial	Venous				
F-11 (cont)	Dogs	0.63%	5		[illegible]0	30	~15 ~9	10 30	Clark and Tinston, 1972a; 1972b
	" "	1.25%	30		[illegible]6	30	~20 ~15	10 30	" " "
	" "	0.1%	10	9.0-13.0	[illegible] - 10.0	10	1.5 - 4.5 (Art) 2.9 - 3.0 (Ven) 0.5 - 1.0 (Art) 0.8 - 1.3 (Ven)	5	Azar *et al.*, 1973
	" "	0.5%	10	14.0-44.0	7.0 - 28.0	10	5.7 - 9.1 (Art) 9.1 - 11.0 (Ven) 2.1 - 3.2 (Art) 0.3 - 3.5 (Ven)	5 5 15 15	" " "
	" "	1.0%	10	36.0-69.0	34.0 - 55.0	7	8.5 - 17.0 (Art) 9.0 - 22.0 (Ven) 2.3 - 4.5 (Art) 4.5 - 7.7 (Ven)	5 5 15 15	" " "
F-12	Rats (anesthetized) (n=2)	0.64%	5		.10 - 3.75	5	0.50 - 0.75 0.03 - 0.03	5 1 hr.	Allen and Hanbury's, Ltd. 1971
	" "	5%	35		~1 (ug/g)	35	~2 (ug/g) <1 (ug/g)	5 10	Griffin *et al.*, 1972
	Dogs	2.4%	5		[illegible]5.00	5	1.10 0.80 0.70 0.12	5 10 15 30	Allen and Hanbury's, Ltd. 1971

Table A-I. (cont.)

Absorption/Elimination Data on Various Fluorocarbons Inhaled from Ambient Air

Fluorocarbon	Species	Concentration in Inhaled Air (%v/v)	Duration of Exposure (minutes)	Peak Blood Levels (ug/ml)		Time to Peak Blood Level (minutes)	Blood Levels After Exposure (ug/ml)	Time to Reduced Level (minutes after termination of exposure)	Reference
				Arterial	Venous				
F-12 (cont)	Dogs	2.52%	5		15.00	5	1.65 0.70 0.30 0.07	5 10 15 30	Allen and Hanbury's, Ltd. 1971
	" "	2.72	5		10.65	5	2.30 0.80 0.55 0.10	5 10 15 30	" " " "
	" "	4.21%	5		14.20	5	5.40 2.20 0.70 0.12	5 10 15 30	" " " "
	" "	4.83%	5		16.25	5	2.50 0.90 0.38 0.25	5 10 15 30	" " " "
	" "	5.01%	5		12.75	5	3.80 1.10 0.75 0.30	5 10 15 30	" " " "
	" "	0.82%	15		8.0	15			Blake and Mergner, 1974
	" "	0.98%	12		7.3	12			" " " "
	" "	0.99%	20		12.7	20			" " " "
	" "	1.01%	15		5.4	15			" " " "

Table A-I. (cont.)

Absorption/Elimination Data on Various Fluorocarbons Inhaled from Ambient Air

Fluorocarbon	Species	Concentration in Inhaled Air (%v/v)	Duration of Exposure (minutes)	Peak Blood Levels (ug/ml) Arterial	Peak Blood Levels (ug/ml) Venous	Time to Peak Blood Level (minutes)	Blood Levels After Exposure (ug/ml)	Time to Reduced Level (minutes after termination of exposure)	Reference
F-11 (cont)	Dogs	0.47%	5		17.50	5	5.40	5	Allen and Hanbury's, Ltd. 1971
							1.45	10	
							1.30	15	
							0.61	30	
	" "	0.49%	5		25.40	5	4.40	5	" " "
							1.40	10	
							0.65	15	
							0.5	30	
	" "	0.91%	5		38.00	5	6.20	5	" " "
							2.70	10	
							0.75	15	
							0.16	30	
	" "	1.14%	5		54.00	5	7.80	5	" " "
							2.95	10	
							2.25	15	
							0.74	30	
	" "	0.47%	23		24.7	23			Blake and Mergner, 1974
	" "	0.53%	20		22.6	20			" " "
	" "	0.55%	19		19.3	19	~6	5	" " "
							~5	10	
							~2.5	30	
	" "	0.63%	5		10	5			Clark and Tinston, 1972a; 1972b
	" "	1.25%	5		20	5			" " "

Table A-I. (cont.)

Absorption/Elimination Data on Various Fluorocarbons Inhaled from Ambient Air

Fluorocarbon	Species	Concentration in Inhaled (%v/v)	Duration of Exposure (minutes)	Peak Blood Level (ug/ml)		Time to Peak Blood Level (minutes)	Blood Levels After Exposure (ug/ml)	Time to Reduced Level (minutes after termination of exposure)	Reference
				Arterial	Venous				
F-12	Dogs	1.18%	20		14.0	15	~3 ~2 <1	5 10 30	Blake and Mergner, 1974
	" "	4%	30		30	20	~8 ~1	10 30	Clark and Tinston, 1972a
	" "	8%	30		~65	30	~15 ~6	10 30	" " " "
	" "	0.1%	10	0.9 - 1.2	0.4 - 1.0	10	<0.1 - 0.2 (Art) <0.1 - 0.3 (Ven) <0.1 - 0.1 (Art) <0.1 (Ven)	5 5 15 15	Azar *et al*., 1973
	" "	5.0%	10	30.0 - 42.0	19.2 - 35.0	10	1.2 - 2.0 (Art) 4.0 - 5.8 (Ven) 0.6 - 0.8 (Art) 2.2 - 3.1 (Ven) 1.2 (Ven)	5 5 10 10 15	" " " "
	" "	10.0%	10	47.0 - 61.0	22.0 - 47.0	10	5.5 - 8.6 (Art) 9.2 - 11.3 (Ven) 0.6 (Art) 1.2 - 5.0 (Ven)	5 5 15 15	" " " "
F-114	Dogs	5%	30		~19	~30	~5 ~1	10 30	Clark and Tinston, 1972a
	" "	10%	30		~40	~10	~10 ~6	10 30	" " " "

Table A-I. (cont.)

Absorption/Elimination Data on Various Fluorocarbons Inhaled from Ambient Air

Fluorocarbon	Species	Concentration in Inhaled Air (%v/v)	Duration of Exposure (minutes)	Peak Blood Levels (ug/ml)		Time to Peak Blood Level (minutes)	Blood Levels After Exposure (ug/ml)	Time to Reduced Level (minutes after termination of exposure)	Reference
				Arterial	Venous				
F-1301 (CF_3Br)	Rats	5%	50		5.6	50	0.62 0.35 0.05 0.07	15 1 hr. 2 hrs. 4 hrs.	Griffin et al., 1972
	Rabbits	5%	30		~15	15 (decline to <10 at ~25 minutes, then ~15 at 30 minutes)	<1	5	" " " "

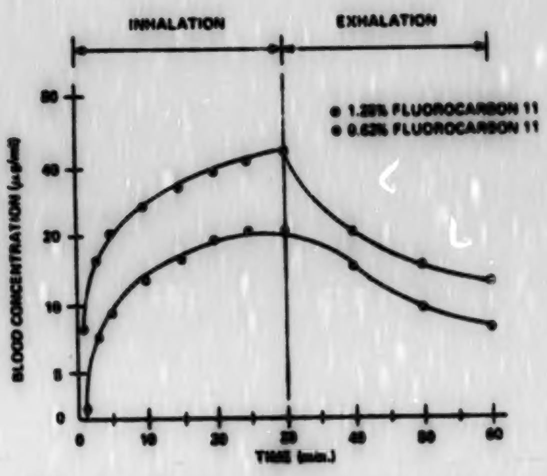

Fig. A-1. Venous blood concentrations of F-11 in dogs exposed to 1.25% or 0.63% F-11 in ambient air for 30 minutes (Clark and Tinston, 1972a).

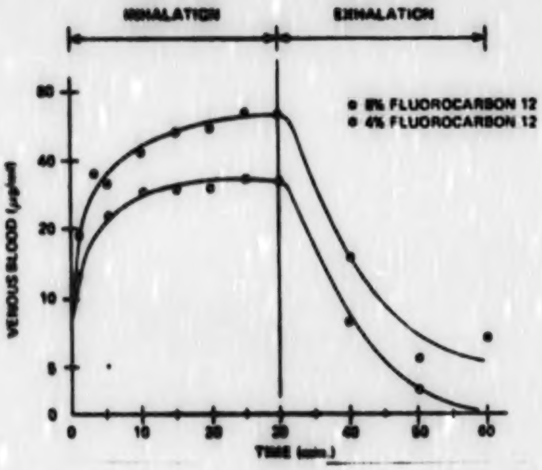

Fig. A-2. Venous blood concentrations of F-12 in dogs exposed to 4% or 8% F-12 in ambient air for 30 minutes (Clark and Tinston, 1972a).

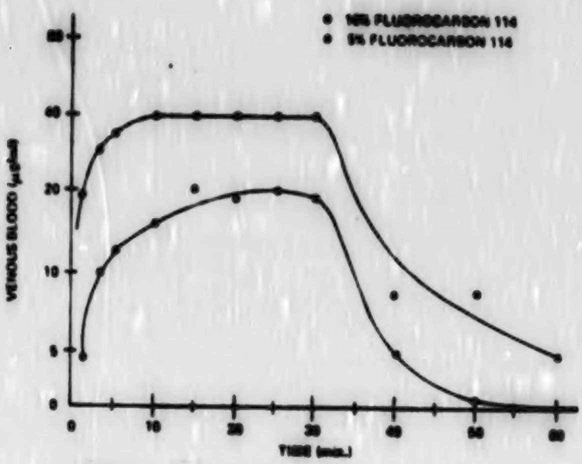

Fig. A-3 Venous blood concentrations of F-114 in dogs exposed to 5% or 10% F-114 in ambient air for 30 minutes (Clark and Tinston, 1972a).

Appendix B: Fluorocarbon Experimental Toxicity Data

Table B-I.

Acute Inhalation Toxicity of Fluorocarbons

Compound	Animal	ALC	LC_{50}	Response Anesth.	Tremors	Non-lethal	Duration	Reference
F-11	Rats	6%					4 hrs.	Maritz, 1971
	Rats	10%					20-30 min.	Lester and Greenberg, 1950
	Rats	20%					5 min.	Kuebler, 1964
	Rats		15%				30 min.	Paulet, 1969
	Rats			10%			20 min.	Kuebler, 1964
	Rats			<9%			N.S.	Lester and Greenberg, 1950
	Rats				33%		N.S.	Maritz, 1971
	Mice		10%				30 min.	Paulet, 1969
	Rabbit		25%				30 min.	Paulet, 1969
	Guinea Pig		25%				30 min	Paulet, 1969
	Guinea Pig					10%	2 hrs.	Clayton, 1966
F-12	Rats		>80%				30 min.	Paulet, 1969
	Rats			50			1 hr.	Kuebler, 1964
	Rats				30-40%		N.S.	Lester and Greenberg, 1950
	Rats					80%	4-6 hrs.	Lester and Greenberg, 1950

Table B-I. (cont.)

Table B-I. Acute Inhalation Toxicity of Fluorocarbons

Compound	Animal	ALC	LC_{50}	Response Anesth.	Tremors	Non-lethal	Duration	Reference
	Mice		76%				30 min.	Paulet, 1969
	Guinea Pigs		>80%				30 min.	Paulet, 1969
	Guinea Pigs					20%	2 hrs.	Clayton, 1966
	Guinea Pigs		>80%				30 min.	Paulet, 1969
	Rabbits		>80%				30 min.	Paulet, 1969
F-11/F-12 (1:1,v/v)	Rats		30%				30 min.	Paulet, 1969
	Mice		22%				30 min.	Paulet, 1969
	Guinea Pigs		50%				30 min.	Paulet, 1969
F-22	Mice	40%					2 hrs.	Clayton, 1966
	Guinea Pigs				10%		2 hrs.	Waritz, 1971
	Guinea Pigs					20%	2 hrs.	Caujolle, 1964
	Dogs	70%		40%			<90 min.	Van Poznak and Artusio, 1960
F-113	Rats	5.5%					4 hrs.	Waritz, 1971
	Rats	8.69%					4 hrs.	Clayton, 1966
	Rats	20%					45 min	Kuebler, 1964
	Rats		11% [some delayed death <2 hrs.]				2 hrs.	Desoille *et al.*, 1968

Table B-I. (cont.)

Table #7. Acute Inhalation Toxicity of Fluorocarbons

Compound	Animal	ALC	LC_{50}	Resp rate Anesth	Tremors	Non-lethal	Duration	Reference
F-113	Rats			15%			15 min.	Kuebler, 1964
	Mice		>10%				30 min.	Raventos and Lemon, 1965
	Mice		9.5%				2 hrs.	Desoille et al., 1968
	Mice			15%			15 min.	Kuebler, 1964
	Mice			5.7% [delayed death with >8%]			30 min.	Raventos and Lemon, 1965
	Guinea Pigs		12%				2 hrs.	Desoille et al., 1968
	Dog				1.3%		6 hrs.	Steinberg et al., 1969
	Dog				1.3%		1 hr.	Steinberg et al., 1969
F-114 ($CClF_2$-$CClF_2$)	Rats	60%					2 hrs.	Moritz, 1971
	Rats			50%			2 hrs.	Kuebler, 1964
	Mice		70% [delayed death ~21 hrs.]				30 min.	Paulet and Desbrousses, 1969
	Mice	[10%: alveolar hemorrhage]					24 hrs.	Quevauviller et al., 1963
	Guinea Pigs					20%	8 hrs.	Yant et al., 1932
	Dogs				20%		2 - 5 min.	Yant et al., 1932

Table B-I. (cont.)

Table B-I. Acute Inhalation Toxicity of Fluorocarbons

Compound	Animal	Response ALC	 LC_{50}	 Anesth.	 Tremors	 Non-lethal	Duration	Reference
F-114a (CF_3-CCl_2F)	Rats	72%					30 min.	Paulet, 1969
	Rats	20% [delayed death]					N.S.	Caujolle, 1964
	Mice		70% [delayed death, 18 hrs.]				30 min.	Paulet and Debrousses, 1969
	Rabbit	75%					30 min.	Paulet, 1969
F-115 (CF_3-$CClF_2$)	Rats					80% (20% O_2)	4 hrs.	Clayton, 1966
F-1301 (CF_3Br)	Rats	80% (in O_2)					30 min.	Caujolle, 1964
	Rat			80% (in O_2)			2 hrs.	Paulet, 1962
	Mice	80% (in O_2)					30 min.	Caujolle, 1964
	Mice	85% (in O_2) [delayed death, 2 days]					2 hrs.	Paulet, 1962
	Mice			80% (in O_2)			2 hrs.	Paulet, 1962
	Guinea Pigs	85% (in O_2) [delayed death, 2 days]					2 hrs.	Paulet, 1962
	Guinea Pigs			80% (in O_2)			2 hrs.	Paulet, 1962
	Rabbits				80% (in O_2)		2 hrs.	Paulet, 1962

Table B-II.

Table B-II. Subacute Inhalation Toxicity of Major Fluorocarbon

Fluorocarbon	Animal	Concentration % (v/v)	Dose Schedule	Mortality	Comments	Reference
F-11	Rats	0.4%	6 hr/day x 28 days	0/[illegible]	No significant signs of toxicity in any animals either during exposure or after 15 days recovery.	Clayton, 1966
	Mice	0.4%	6 hr/day x 28 days	0/8		
	Guinea Pigs	0.1%	6 hr/day x 28 days	0/2		
	Rabbits	0.4%	6 hr/day x 28 days	0/1		
	Rats	1.2%	4 hr/day x 10 days	0/4	Slight respiratory increase twitching, chewing motion; rapid recovery after exposure. Pathology: Brain-neuronal edema and neuronolial vacuol: Liver-vacuolation of cells; Lungs - emphysema and edema; Spleen-increased hematopoiesis.	Clayton, 1966
	Dogs	1.25%	3.5 hr/day x 20 day	0/2	No signs of toxicity.	Clayton, 1966
	Cats	2.5%	3.5 hr/day x 20 days	0.2		
	Guinea Pigs	2.5%	3.5 hr/day x 20 day	0/3		
	Rats	2.5%	3.5 hr/day x 20 day	0/5		
F-12	Cats	10%	3.5 hr/day x 20 day	0/2	No signs of toxicity	Clayton, 1966
	Guinea pigs	10%	3.5 hr/day x 20 day	0/3		
	Rats	10%	3.5 nr/day x 20 day	0/5		
	Dogs	10%	3.5 hr/day x 20 day	0/2		

Table B-II. (cont.)

Table B-II. Subacute Inhalation Toxicity of Major Fluorocarbon

Fluorocarbon	Animal	Concentration % (v/v)	Dose Schedule	Mortality	Comments	Reference
F-113	Cats	1.25%	3.5 hr/day x 20 days	0/2	No signs of toxicity.	Clayton, 1966
	Dogs	1.25%	3.5 hr/day x 20 days	0/2		
	Guinea Pigs	2.5%	3.5 hr/day x 20 days	0.2		
	Rabbits	1.1%	2 hr/day, 5 days/wk x 120 1080 days	0.6	No variation from controls	Desoille *et al.*, 1968
	Rats	1.2%	2 hr/day, 365-730 day 5 days/wk.	3/6	Deaths not associated with exposure. Slight sleepiness during exposure.	Desoille *et al.*, 1968
	Rats	0.2%	24 hr/day x 14 days	0/50	Rat kidneys increased in weight above controls; enlarged thyroid gland in all monkeys exposed. Neighter effect conclusively attributed to exposure.	Carter *et al.*, 1970
	Mice	0.2%	24 hr/day x 14 days	0/40		
	Dogs	0.2%	24 hr/day x 14 days	0/8		
	Monkeys	0.2%	24 hr/day x 14 days	0.4		
	Dogs	0.51%	6 hr/day, 5 days/wk. x 4 wk.	0/4	No toxic effects.	Steinberg *et al.*, 1969
	Guinea pigs	0.51%	6 hr/day, 5 days/wk. x 4 wk.	0/10		
	Rats	0/51%	6 hr/day, 5 days/wk x 4 wk.	0/20		
	Rats	6%	1 hr/day x 5 days	0/5	Liver: two rats showed fair amount of fat in Kupffer cell possibly indicative of change in lipids or lipoproteins; not definitely attributable to exposure.	Burn *et al.*, 1959

Table B-II. (cont.)

Table B-II. Subacute Inhalation Toxicity of Major Fluorocarbon

Fluorocarbon	Animal	Concentration % (v/v)	Dose Schedule	Mortality	Comments	Reference
F-113 (cont)	Rats	40%	1 hr/day x 5 days	0/4	Mildly toxic effect in liver. Moderate degree of mitotic activity in liver cell of one rat; others showed similar activity to a lesser degree.	Burn _et al_., 1959
F-114	Cats	10%	3.5 hr. day x 20 days	0/2	No signs of toxicity	Clayton, 1966
	Guinea Pigs	10%	3.5 hr/day x 20 days	0/3		
	Rats	10%	3.5 hr/day x 20 days	0/6		
	Dogs	10%	3.5 hr/day x 20 days	0/2		
	Mice	10%	2.5 hr/day, 5 days/wk x 10 days	0/10	No signs of toxicity	Paulet and Desbrousses, 1959
	Rats	10%	2.5 hr/day, 5 days/wk x 10 days	0/10		
	Mice	20%	2.5 hr/day, 5 days/wk x 10 days	0/10	Exudative and congested lesions of the alveoli and bronchioles without cell structure alteration.	
	Rats	20%	2.5 hr/day, 5 days/wk x 10 days	0/10	Slight decrease in equilibrium.	
	Rats	1%	2.5 hr/day, 5 days/wk x 50 days	0/30	No toxic effects	Quevauviller, _et al_., 1963
	Guinea Pigs	14.16%	8 hr/day x 21 days	1/8	No signs of toxicity. Death not related to exposure. Occasional slight fatty degeneration of liver.	Vant _et al_., 1932

Table B-II. (cont.)

Table B-I' Subacute Inhalation Toxic t of Major Fluorocarbon

Fluorocarbon	Animal	Concentration % (v/v)	Dose Schedule	Mortality	Comments	Reference
F-114 (cont)	Guinea pigs	20%	8 hr/day x 4 days	0/6	Ruffled fur and occasional convulsive jerk. Increase in excreta.	Vant et al., 1932
	Guinea pigs	20%	8 hr/day x 2 days	0/10		
	Dogs	14.16%	8 hr/day x 3 days	0/1	Salivation and wretching.	
	Dogs	14.16%	8 hr/day x 21 days	0/2	Occasional convulsions with tremors during first three days, followed by definite development of tolerance to exposure. Increase in hemoglobin, red blood cells, and younger forms of polymorphonuclear leucocytes.	
	Dogs	20%	8 hr/day x 3-4 days	4/4	All died during exposure. Effects same as above but more severe. Pathology as follows. Brain-congestion of meningeal vessels; Heart - mypcardium, congested; liver -very marked congestion; kidney - congested, pale yellowish glandular cortex; gastrointestinal tract - gastric and duodenal mucosa markedly congested and swollen. One dog had suggestion of duodenal ulcer.	
	Rats	1%	2 hr/day, 5 days/wk. x ~184 days	2/6	Small increase in number of red blood cells in rats.	Desoille et al., 1973
	Rabbits	12%	2 hr/day, 5 days/wk. x ~207 days	0/6	No signs of toxicity	Desoille et al., 1973

Table B-II. (cont.)

Table B-II. Subacute Inhalation Toxici y of Major Fluorocarbon

Fluorocarbon	Animal	Concentration % (v)	Dose Schedule	Mortality	Comments	Reference
F-13B1	Mice	50%	2 hr/day x 15 days	1/2	Death not related to exposure	Paulet, 1966
	Rats	50%	2 hr/day x 15 days	0		
	Guinea pigs	50%	2 hr/day x 15 days	1/10	Death not related to exposure	
Mixture F-12(48.9%) F-11 (25%) F-114 (25%) F-113(1.1%)	Mice	970 mg/kg/day	5 min. exposure in a chamber, twice daily 5 day/wk. x 23 mant	0/30	No signs of toxicity	Smith and Case, 1973
Mixture F-12 (40%) F-114 (50%) Ethyl alcohol (10%)	Rats	164 mg/kg/day	5 min. exposure in chamber, twice daily, 7 days.wk. x 93 day	0/16	No signs of toxicity	
Mixture F-21 - $(CHCl_2F)$ (40%) F-22 (60%)	Puppies	1714 mg/kg/day	5 min. exposures in chamber, twice daily 5 days/wk. x 2 wks.	0/2	Sedate and ataxic during exposure	
Mixture F-12 (40%) F-114(50%) Ethyl alcohol (10%)	Dogs	700 mg/kg/day	Exposure by face ma , twic daily, 7 days/wk x 93 days	0/4	No signs of toxicity	

Table B-II. (cont.)

Table B-II. Subacute Inhalation Toxicity of Major Fluorocarbon

Fluorocarbon	Animal	Concentration % (v/v)	Dose Schedule	Mortality	Comments	Reference
Mixture F-12 (50%) F-114(25%) F-11(24.5%) Span 85 (0.5%)	Dogs	560 mg/kg/day	Exposure by face mask twice daily, 7 days/w x 90 days.	0/4	No signs of toxicity	Smith and Case, 1973
Mixture (as above)	Dogs	2240 mg/kg/day	Exposure by face mask twice daily, 7 days/w x 1 year	0/6	Occasional slight depression or drowsiness immediately after dosing, lasting only minutes.	

Table B-III.

Table B-III. Chronic Inhalation Toxicity of Major Fluorocarbon

Fluorocarbon	Animal	Concentration % (v/v)	Dose Schedule	Mortality	Comments	Reference
F-11	Rats	1.025%	8 hr/day x 30 days	0/15	No outward signs of toxicity. (See text for discussion.)	Jenkins et al., 1970
	Guinea pigs	1.025%	8 hr/day x 30 days	0/15		
	Dogs	1.025%	8 hr/day x 30 days	0/2		
	Monkeys	1.025%	8 hr/day x 30 days	0/9		
	Rats	0.1%	24 hr/day x 90 day	0/15		
	Guinea pigs	0.1%	24 hr/day x 90 day	0/15		
	Dogs	0/1%	24 hr/day x 90 day	0/2		
	Monkeys	0/1%	24 hr/day x 90 day	1/9	Hemorrhagic lesions on surface of lung not directly attributable to exposure.	
F-12	Dogs	20%	7-8 hr/day x 52 days	0/2	Dogs and monkeys apparently developed tolerance to exposure, tremors disappearing after two weeks. Guinea pigs deaths not related to exposure (see text).	Sayer et al., 1930
	Monkeys	20%	7-8 hr/day x 35-53 days	0/2		
	Guinea pigs	20%	7-8 hr/day x 35-56 days	1[illegible]26		
	Rats	0.084%	8 hr/day, 5 days/w x 30 days	1/15	Several guinea pigs showed focal necrosis or fatty infiltration of liver; one monkey had heavy pigment deposits in liver, spleen and kidney.	Prendergast et al., 1967
	Guinea pigs	0.084%	8 hr/day, 5 days/w x 30 days	0/15		
	Rabbits	0.084%	" " "	0/3		
	Dogs	0.084%	" " "	1/2		
	Monkeys	0.084%	" " "	0/3		

Table B-III. (cont.)

Table B-III. Chronic Inhalation Toxicity of Fluorocarbons (cont.)

Fluorocarbon	Animal	Concentration	Dose Schedule	Mortality	Comments	
F-12 (cont)	Rats	0.081%	24hr/day X 90 days	2/15	Guinea pigs all showed slight to excessive fatty infiltration of liver and several had focal or submassive necrosis of liver (see text.)	Prendergast *et al.*, 1967
	Guinea pigs	0.081%	24hr/day X 90 days	1/15		
	Rabbits	0.081%	24hr/day X 90 days	0/3		
	Dogs	0.081%	24hr/day X 90 days	0/2		
	Monkeys	0.081%	24hr/day X 90 days	0/3		
F-22	Rabbits	1.42%	6hr/day X 10 months	N.S.	(see text.)	Clayton, 1966
	Rats	1.42%	6hr/day X 10 months	N.S.		
	Mice	1.42%	6hr/day X 10 months	N.S.		
	Rats	0.198%	6hr/day X 10 months	N.S.	No toxic effects	Clayton, 1966
	Mice	0.198%	6hr/day X 10 months	N.S.		
F-113	Rats	0.0252%	7hr/day X 30 days	0/21	No toxic effects	Clayton, 1966
	Rats	0.5%	7hr/day X 30 days	0/12	Three rats showed slightly pale livers	Clayton, 1966
F-115	Rats	10%	6hr/day. 5 days/wks. X 90 days	0/20	No toxic effects	Clayton, 1966
	Mice	10%	6hr/day. 5 days/wks. X 90 days	0/10		
	Rabbits	10%	6hr/day 5 days/wks. X 90 days	0/4		
	Dogs	10%	6hr/day. 5 days/wks. X 90 days	0/4		
F-1381	Rats	2.3%	6hr/day 90 days	0/30	No toxic effects	Clayton, 1966
	Dogs	2.3%	6hr/day 90 days	0/3		

Appendix C: Fluorocarbon Cardiovascular Effects Data

Table C-I.

Table C-I. Induction of Cardiac Arrhythmias by Fluorocarbons

Fluorocarbon	Species (number)	Concentration (% by volume) and Duration	Type of Arrhythmia (Incidence)	Reference
F-11	Mice (3)[a]	2% x 6 min.	None	Aviado and Belej (1974)
	Mice (3)[a]	5% x 6 min.	None	Aviado and Belej (1974)
	Mice (5)[a]	10% x 6 min.	2nd degree AV block (4) 3rd degree AV block (1)	Aviado and Belej (1974)
	Rats[a]	2.5%	Bradychardia	Doherty and Aviado (1975)
	Rats[a]	5.0%	Bradychardia	Doherty and Aviado (1975)
	Rats[a]	10%	Bradychardia and ectopic beats (77.8%)	Doherty and Aviado (1975)
	Rats[b]	5.0%	Bradychardia	Doherty and Aviado (1975)
	Rats[b]	10.0%	Bradychardia and ectopic beats (14.3%)	Doherty and Aviado (1975)
	Rats[b]	20.0%	Bradychardia and ectopic beats (100%)	Doherty and Aviado (1975
	Rats (5)[c]	2.5% x 5 min.	Tachychardia, atrial fibrillation, ventricular extrasystoles (1)	Watanabe and Aviado (1975)
	Rats (5)[c]	5.0% x 5 min.	Tachychardia, atrial fibrillation, ventricular extrasystoles (2)	Watanabe and Aviado (1975)

Table C-I. (cont.)

Table C-I. Induction of Cardiac Arrhythmias by Fluorocarbons (cont)

Fluorocarbon	Species (number)	Concentration (% by volume) and Duration	Type of Arrhythmia (Incidence)	Reference
F-11	Rats (5)^{c}	10% x 5 min.	Tachychardia, atrial fibrillation, ventricular extrasystoles (4)	Watanabe and Aviado (1975)
	Rats (4)^{a}	2.5% x 5 min.	0 arrhythmias, no change in heart rate	Watanabe and Aviado (1975)
	Rats (4)^{a}	5.0% x 5 min.	1 arrhythmia, no change in heart rate	Watanabe and Aviado (1975)
	Rats (4)^{a}	10% x 5 min.	4 arrhythmias, no change in heart rate	Watanabe and Aviado (1975)
	Monkeys (7)^{a}	2.5% x 5 min.	Tachycardia	Belej *et al*. (1974)
	Monkeys (7)^{a}	5.0% x 5 min.	Tachcardia; ventricular premature beats; AV block (29%)	Belej *et al*. (1974)
F-12	Mice (3)^{a}	40% x 6 min.	None	Aviado and Belej (1974)
	Mice (3)^{a}	60% x 6 min.	None	Aviado and Belej (1974)
	Rats^{a}	5%	None	Doherty and Aviado (1975)
	Rats^{a}	10%	Arrhythmias (10%)	Doherty and Aviado (1975)
	Rats^{a}	20%	Bradychardia and arrhythmias (10%)	Doherty and Aviado (1975)

Table C-I. (cont.)

Table C-I. Induction of Cardiac Arrhythmias by Fluorocarbons (cont)

Fluorocarbon	Species (number)	Concentration (% by volume) and Duration	Type of Arrhythmia (Incidence)	Reference
F-12	Rats^b	10%	Bradychardia	Doherty and Aviado (1975)
	Rats^b	20%	Bradychardia	Doherty and Aviado (1975)
	Rats^b	40%	Bradychardia and arrhythmias (16.7%)	Doherty and Aviado (1975)
	Rats (5)^c	10%	Tachycardia, no arrhythmias	Watanabe and Aviado (1975)
	Rats (5)^c	20%	Tachycardia, no arrhythmias	Watanabe and Aviado (1975)
	Rats (4)^c	40%	Tachycardia, no arrhythmias	Watanabe and Aviado (1975)
	Rats (4)^a	10%	0 arrhythmias, no change in heart rate	Watanabe and Aviado (1975)
	Rats (4)^a	20%	0 arrhythmias, no change in heart rate	Watanabe and Aviado (1975)
	Rats (4)^a	40%	1 arrhythmia, no change in heart rate	Watanabe and Aviado (1975)
	Monkeys (3)^a	5.0% x 5 min.	None	Belej _et_ _al_. (1974)
	Monkeys (3)^a	10% x 5 min.	Arrhythmias	Belej _et_ _al_. (1974)
F-22	Mice (3)^a	20% x 6 min.	None	Aviado and Belej (1974)

Table C-I. (cont.)

Table C-I. Induction of Cardiac Arrhythmias by Fluorocarbons (cont)

Fluorocarbon	Species (number)	Concentration (% by volume) and Duration	Type of Arrhythmia (Incidence)	Reference
F-22	Mice (7)^a	40% x 6 min.	None	Aviado and Belej (1974)
	Monkeys (3)^a	10% x 5 min.	None	Belej *et al*. (1974)
	Monkeys (3)^a	20% x 5 min.	None	Belej *et al*. (1974)
F-113	Mice (3)^a	5.0% x 6 min.	None	Aviado and Belej (1974)
	Mice (3)^a	10% x 6 min.	Inverted T wave (1)	Aviado and Belej (1974)
	Monkeys (3)^a	2.5% x 5 min.	None	Belej *et al*. (1974)
	Monkeys (3)^a	5.0% x 5 min.	Tachycardia and arrhythmia	Belej *et al*. (1974)
F-114	Mice^a	10%,20% or 40% x 5 min.	None	Aviado and Belej (1974)
	Monkeys^a	5% x 5 min.	None	Belej *et al*. (1974)
	Monkeys^a	10% or 20% x 5 min.	Tachycardia and arrhythmia	Belej *et al* (1974)
F-11[illegible]	Mice^a	10%,20% or 40% x 5 min.	None	Aviado and Belej (1974)
	Monkeys^a	10% or 20% x 5 min	None	Belej *et al*. (1974)
F-142b (Chlorodifluoro-ethane)	Mice^a	40% or 60% x 6 min	None	Aviado and Belej (1974)

Table C-I. (cont.)

Table C-I. Induction of Cardiac Arrhythmias by Fluorocarbons (cont)

Fluorocarbon	Species (number)	Concentration (% by volume) and Duration	Type of Arrhythmia (Incidence)	Reference
F-142b (Chlorodifluoroethane)	Monkeys[a]	5% or 10% x 5 min.	None	Belej *et al*. (1974)
F-152a (Difluoroethane)	Mice[a]	20% or 40% x 5 min.	None	Aviado and Belej (1974)
	Rats[a]	5%	Arrhythmias (10%)	Doherty and Aviado (1974)
	Rats[a]	10%	Arrhythmias (10%)	Doherty and Aviado (1974)
	Rats[a]	20%	Arrhythmias (16.7%)	Doherty and Aviado (1974)
	Rats[b]	10%, 20% or 40%	None	Doherty and Aviado (1974)
	Rats (4)[a]	40%	Arrhythmia (1)	Watanabe and Aviado (1975)
	Rats (5)[c]	40%	None	Watanabe and Aviado (1975)
F-21	Mice (3)[a]	50% x 6 min.	None	Aviado and Belej (1974)
	Mice (4)[a]	10% x 6 min.	2nd degree AV block (1)	Aviado and Belej (1974)
	Mice (10)[a]	20% x 6 min.	2nd degree AV block (9)	Aviado and Belej (1974)

Table C-I. (cont.)

Table C-I. Induction of Cardiac Arrhythmias by Fluorocarbons (cont)

Fluorocarbon	Species (number)	Concentration (% by volume) and Duration	Type of Arrhythmia (Incidence)	Reference
F-21	Monkeys (3)[a]	2.5% x 5 min.	None	Belej *et al*. (1974)
	Monkeys (3)[a]	5.0% x 5 min.	Arrhythmias	Belej *et al*. (1974)

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[a] Anaesthetized

[b] Anaesthetized and adrenalectomized

[c] Unanaesthetized

Table C-II.

Table C-I . Fluorocarbon Sensitization to Arrhythmias from Injected Epinephrine

Fluorocarbon	Species	Concentration (% by Volume) and Duration	Dose of Epinephrine	Type of Arrhythmia (Incidence)	Minimum Concentration of Fluorocarbon Eliciting Arrhythmia without Epinephrine	Reference
F-11	Mice	2% x 5 min.	6 µg/kg	0/3		Aviado & Belej (1974)
		5% x 5 min.	6 µg/kg	2nd degree AV block (3/3)	10%	
	Dogs	.09-.13% x 5 min.	8 µg/kg in 9 sec.	0/12	Not tested	Reinhardt *et al*. (1971)
		.35-.61% x 5 min.	8 µg/kg in 9 sec.	Ventricular fibrillation (1/12)		
		.96-1.21* x 5 min.	8 µg/kg in 9 sec.	Arrhythmias (5/12; 3 with ventricular fibrillation)		
	Monkeys	2.5% x 5 min.	0.5 µg/kg/min.	Arrhythmias	5.0%	Belej *et al*. (1974)
F-12	Mice	20% or 40% x 5 min.	6 µg/kg	None	Does not elicit arrhthmias in mice at 40%	Aviado & Belej (1974)
	Dogs	2.5% x 5 min.	8 µg/kg in 9 sec.	None	Not tested	Reinhardt *et al*. (1971)
		5.0% x 5 min.	8 µg/kg in 9 sec.	Arrhythmias (5/12; 1 with ventricular fibrillation)		
	Monkeys	5% x 5 min.	0.5 µg/kg/min.	None	10%	Belej *et al*. (1974)

Table C-II. (cont.)

Table C-II. Fluorocarbon Sensitization to Arrhythmias from Injected Epinephrine (cont.)

Fluorocarbon	Species	Concentration (% by Volume) and Duration	Dose of Epinephrine	Type of Arrhythmia (Incidence)	Minimum Concentration of Fluorocarbon Eliciting Arrhythmia without Epinephrine	Reference
F-22	Mice	20% x 5 min.	6 μg/kg	3/3	Does not elicit arrhythmias in mice at 40%	Aviado & Belej (1974)
		40% x 5 min.	6 μg/kg	2nd degree AV block (3/5)		
	Dogs	2.5% x 5 min.	8 μg/kg in 9 sec.	1/12	Not tested	Reinhardt *et al.* (1971)
		[illegible].0% x 5 min.	8 μg/kg in 9 sec.	Arrhythmias (2/12; no ventricular fibrillation)		
F-113	Mice	5% x 5 min.	6 μg/kg	Ventricular ectopics (1/3)	10%	Aviado & Belej (1974)
		10% x 5 min.	6 μg/kg	Ventricular bigeminy (3/3)		
	Dogs	0.21-0.25% x 5 min.	8 μg/kg in 9 sec.	/12	Not tested	Reinhardt *et al.* (1973)
		0.46-0.56% x 5 min.	8 μg/kg in 9 sec.	[illegible] 8		
		0.97-1.16% x 5 min.	8 μg/kg in 9 sec.	2/12 (1 ventricular fibrillation and cardiac arrest)		
F-114	Mice	10% x 5 min.	6 μg/kg	[illegible]	Does not elicit arrhythmias in mice at 40%	Aviado & Belej (1974)
		20% x 5 min.	6 μg/kg	[illegible] degree AV block (1/4)		
		40% x 5 min.	6 μg/kg	[illegible] degree AV block (2/3)		
	Dogs	2.5% x 5 min.	8 μg/kg in 9 sec.	/12	Not tested	Reinhardt *et al.* (1971)
		5.0% x 5 min.	8 μg/kg in 9 sec.	/12 (2 ventricular fibrillation and cardiac arrest)		

Table C-II. (cont.)

Table C-II Fluorocarbon Sensitization to Arrhythmias from Injected Epinephrine (cont.)

Fluorocarbon	Species	Concentration (% by Volume) and Duration	Dose of Epinephrine	Type of Arrhythmia (Incidence)	Minimum Concentration of Fluorocarbon Eliciting Arrhythmia without Epinephrine	Reference
F-115	Mice	13% x 5 min.	6 ug/kg	0/3	Does not elicit arrhythmias in mice at 40%	Aviado and Belej (1974)
		20% X 5 min.	"	2nd degree AV block (2/4) Ventricular fibrillation (1/4); ventricular ectopics (1/4).		
		40% X 5 min.	"			
	Dogs	15% X 5 min.	8 ug/kg in 9 sec.	1/13	Not tested	Reinhardt _et al_. (1971)
		25% X 5 min	"	4/12 (no ventricular fibrillations		
F-133a	Dogs	5% X 5 min	8-10 ug/kg	0/62	Not tested	Reinhardt and Reinke (1972)
		7.5% X 5 min.	"	1/18 (5.6%)		
		10% X 5 min.	"	8/69 (11.6%		
		15% X 5 min	"	2/7 (28.6%)		
		20% X 5 min	"	8/13 (61.5%)		
F-142b (Chlorodifluoroethane)	Mice	40% or 60% X 5 min.	6 ug/kg	None	Does not elicit Arrhythmias in mice at 60%	Aviado and Belej (1974)
	Dogs	2.5% X 5 min.	8 ug/kg in 9 sec	0/6	Not tested	Reinhardt _et al_ (1971)
		5.0% X 5 min.	"	5/12		
		10% X 5 min.	"	12/12		

Table C-II. (cont.)

Table C-II. Fluorocarbon Sensitization to Arrhythmias from Injected Epinephrine (cont.)

Fluorocarbon	Species	Concentration (% by Volume) and Duration	Dose of Epinephrine	Type of Arrhythmia (Incidence)	Minimum Concentration of Fluorocarbon Eliciting Arrhythmia without Epinephrine	Reference
F-152a (difluoroethane)	Mice	20% or 40% x 5 min.	6 µg/kg	None	Does not elicit arrhythmias in mice at 40%	Aviado & Belej (1974)
	Dogs	5% x 5 min.	8 µg/kg in 9 sec.	0/12	Not tested	Reinhardt *et al.* (1971)
		15% x 5 min.	8 µg/kg in 9 sec.	3/12		
F-21	Mice	5% x 5 min.	6 µg/kg	0/3	10%	Aviado & Belej (1974)
		10% x 5 min.	6 µg/kg	2nd degree AV block (6/6)		

Table C-III.

Table C-III. Summary of Bronchopulmonary and Cardiovascular Effects other than Arrhythmia[a]

Fluorocarbon	Tachycardia		Myocardial Depression		Hypotension	
	Dog	Monkey	Dog	Monkey	Dog	Monkey
F-11	$(1)^{+++}$	$(2.5)^{++}$	$(2.5)^{++}$	$(2.5)^{++}$	$(2.5)^{++}$	$(2.5)^{++}$
F-12	$(10)^{+}$	$(10)^{+}$		$(10)^{+}$	0	$(10)^{+}$
F-22		$(20)^{+}$		$(20)^{+}$		$(20)^{+}$
F-113		$(5.0)^{+}$	$(5.0)^{+}$	$(5.0)^{+}$		$(5.0)^{+}$
F-114	$(10)^{+}$	$(10)^{+}$		$(10)^{+}$	$(20)^{+}$	$(10)^{+}$
F-115	$(20)^{+}$	0	$(20)^{+}$	0	$(20)^{+}$	0
F-21	$(2.5)^{++}$	$(5.0)^{+}$		$(5.0)^{+}$	$(10)^{+}$	$(5.0)^{+}$
F-142b	$(20)^{+}$	0		$(10)^{+}$	$(10)^{+}$	$(20)^{+}$
F-152a	0	0	$(20)^{+}$	0	0	0

Table C-III. (cont.)

Table C-III-Summary of Bronchopulmonary and Cardiovascular Effects other than Arrhythmia[a] (continued)

Fluorocarbon	Early Respiratory Depression				Bronchoconstriction				Decreased Compliance			
	Mouse	Rat	Dog	Monkey	Mouse	Rat	Dog	Monkey	Mouse	Rat	Dog	Monkey
F-11	(2.5)$^{++}$	(2.5)$^{++}$	(10)$^{+}$	(5.0)$^{+}$	(1)$^{++}$	2.5)$^{++}$	0	0	(1)$^{++}$	(2.5)$^{++}$	0	0
F-12	(5.0)$^{+}$	(10)$^{+}$	(20)$^{+}$	(0)$^{+}$	(2)$^{+}$	[illegible]	(10)$^{+}$	(10)$^{+}$	(2)$^{+}$	(10)$^{+}$	(20)$^{+}$	(10)$^{+}$
F-22				(20)$^{+}$				(20)$^{+}$				0
F-113				0				0				0
F-114		0	0	(20)$^{+}$		(10)$^{+}$	(10)$^{+}$	(20)$^{+}$		(10)$^{+}$	(5)$^{+}$	0
F-115		0	0	0		10)$^{++}$	(10)$^{+}$	0		(10)$^{+}$	(20)$^{+}$	0
F-21		(2.5)$^{++}$	0	(2.5)$^{++}$		0	(2.5)$^{++}$	0		0	(2.5)$^{++}$	0
F-142b			0	0			(10)$^{+}$	0			0	0
F-152a	(5.0)$^{+}$		0	0	(2)$^{+}$		0	0		(2)$^{+}$	0	0

a) Data from Aviado (1975b) and Aviado (1975c)
Numbers in parentheses are approximate minimal inhaled concentration (% [illegible] volume) eliciting the effect; 0 indicates absent or opposite responses;
+, ++, +++ indicate intensity of response

Table D-I.

Fluorocarbon Numbers and Molecular Formulae of the Major One and Two Carbon Saturated Fluorocarbons

Fluorocarbon Number*	Chemical Name	Molecular Formula
F-11	Trichlorofluoromethane	CCl_3F
F-12	Dichlorodifluoromethane	CCl_2F_2
F-13	Chlorotrifluoromethane	$CClF_3$
F-14	Tetrafluoromethane	CF_4
F-21	Dichlorofluoromethane	$CHCl_2F$
F-22	Chlorodifluoromethane	$CHClF_2$
F-23	Trifluoromethane	CHF_3
F-113	Trichlorotrifluoroethane	$CCl_2F\text{-}CClF_2$
F-114	Dichlorotetrafluoroethane	$CClF_2\text{-}CClF_2$
F-115	Chloropentafluoroethane	$CClF_2\text{-}CF_3$
F-142b	Chlorodifluoroethane	$CClF_2\text{-}CH_3$
F-152a	Difluoroethane	$CHF_2\text{-}CH_3$
F-13B1	Bromotrifluoromethane	$CBrF_3$
(Halothane)	Bromochlorotrifluoroethane	$CBrClH\text{-}CF_3$

* See Introduction for description of fluorocarbon numbering system.